06-23-00 A

Please type a plus sign (+) inside this box. → ☒ BOX-SEQ PTO/SB/05 (2/98)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	LUD 5615.1 CIP (10006411)
First Inventor or Application Identifier	DIRK JAEGER
Title	ISOLATED NUCLEIC ACID MOLECULES ENCODING CANCER ASSOCIATED ANTIGENS
Express Mail Label No.	EL227322248US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ *Fee Transmittal Form *(e.g., PTO/SB/17)* *(Submit an original and a duplicate for fee processing)*
2. ☒ Specification *(preferred arrangement set forth below)* — *Total Pages* 39
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Reference of Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. ☒ Drawing(s) *(35 U.S.C. 113)* — *Total Sheets* 2
4. ☒ Oath or Declaration (UNSIGNED) — *Total Pages* 2
   a. ☐ Newly executed (original or copy) (UNSIGNED)
   b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d)) *(for continuation/divisional with Box 17 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33 (b)
5. ☒ Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be a part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

6. ☐ Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☐ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. ☐ *Small Entity Statement(s) (PTO/SB/09-12) ☐ Statement filed in prior application, Status is proper and desired
15. ☐ Certified Copy of Priority Document(s)
16. ☐ Other:

NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STSTEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28)

17. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*

☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No: 09/451,739

Prior application information: Examiner: UNKNOWN Group / Art Unit UNKNOWN

18. CORRESPONDENCE ADDRESS

☐ Customer Number or bar code label *(Insert Customer No. or Attach bar code label here)* or ☐ Correspondence address below

Name	FULBRIGHT & JAWORSKI LLP				
Address	666 FIFTH AVENUE				
City	NEW YORK	State	NEW YORK	ZIP Code	10103
Country	USA	Telephone	212-318-3000	Fax	212-318-3400

Name (Print/Type)	NORMAN D. HANSON	Registration No. (Attorney/Agent)	30,946
Signature	Norman D. Hanson	Date	6/22/2000

VIA EXPRESS MAIL
"Express Mail" mailing label Number EL227322248US
Date of Deposit June 22, 2000
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under CFR 1.10 on the date indicated above, and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231
FULBRIGHT & JAWORSKI L.L.P.
By: Denise Lewis

LUD 5615.1-JEL/NDH (09905230)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Jager, et al.
Serial No.	:	Continuation In Part of Serial No. 09/451,739
Filed	:	Herewith
For	:	Isolated Nucleic Acid Molecules Encoding Cancer Associated Antigens, The Antigens Per Se, and Uses Thereof
Group Art Unit	:	Not Assigned
Examiner	:	Not Assigned

June 22, 2000

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

S I R:

Prior to examination, please amend this application as follows:

IN THE CLAIMS

Cancel claims 1-80 without prejudice.

Add claims 81-157 which follow:

Claim 81: An isolated nucleic acid molecule which encodes a cancer associated antigen, the complementary sequence of which hybridizes, in whole or in part, to at least one of a nucleic acid molecule, the nucleotide sequence consists of the nucleotide sequence of SEQ ID NO: 15, SEQ ID NO: 22, or SEQ ID NO: 26.

Claim 82: The isolated nucleic acid molecule of claim 81, the nucleotide sequence of which comprises the nucleotide sequence of SEQ ID NO: 15, SEQ ID NO: 22, or SEQ ID NO: 26.

Claim 83: The isolated nucleic acid molecule of claim 82, comprising the nucleotide sequence of SEQ ID NO: 15.

Claim 84: The isolated nucleic acid molecule of claim 82, comprising the nucleotide sequence of SEQ ID NO: 22.

Claim 85: The isolated nucleic acid molecule of claim 82, comprising the nucleotide sequence of SEQ ID NO: 26.

Claim 86: Expression vector comprising the isolated nucleic acid molecule of claim 81, operably linked to a promoter.

Claim 87: Eukaryotic cell line or prokaryotic cell strain, transformed or transfected with the expression vector of claim 86.

Claim 88: Eukaryotic cell line or prokaryotic cell strain, transformed or transfected with the isolated nucleic acid molecule of claim 81.

Claim 89: Isolated cancer associated antigen comprising all or part of the amino acid sequence encoded by SEQ ID NO: 15, 22 or 26.

Claim 90: The eukaryotic cell line or prokaryotic cell strain of claim 88, wherein said cell line is also transfected with a nucleic acid molecule coding for a cytokine.

Claim 91: The eukaryotic cell line or prokaryotic cell strain of claim 90, wherein said cell line is further transfected by a nucleic acid molecule coding for an MHC molecule.

Claim 92: The eukaryotic cell line or prokaryotic cell strain of claim 90, wherein said cytokine is an interleukin.

Claim 93: The eukaryotic cell line or prokaryotic cell strain of claim 92, wherein said interleukin is IL-2, IL-4 or IL-12.

Claim 94: The eukaryotic cell line or prokaryotic cell strain of claim 88, wherein said cell line has been rendered non-proliferative.

Claim 95: The eukaryotic cell line of claim 88, wherein said cell line is a fibroblast cell line.

Claim 96: Expression vector comprising a mutated or attenuated virus and the isolated nucleic acid molecule of claim 81.

Claim 97: The expression vector of claim 96, wherein said virus is adenovirus or vaccinia virus.

Claim 98: The expression vector of claim 97, wherein said virus is vaccinia virus.

Claim 99: The expression vector of claim 97, wherein said virus is adenovirus.

Claim 100: Expression system useful in transfecting a cell, comprising (i) a first vector containing a nucleic acid molecule which codes for the isolated cancer associated antigen of claim 89 and (ii) a second vector selected from the group consisting of (a) a vector containing a nucleic acid molecule which codes for an MHC or HLA molecule which presents an antigen

derived from said cancer associated antigen and (b) a vector containing a nucleic acid molecule which codes for an interleukin.

Claim 101: Immunogenic composition comprising the isolated cancer antigen of claim 89, and a pharmaceutically acceptable adjuvant.

Claim 102: The immunogenic composition of claim 101, wherein said adjuvant is a cytokine, a saponin, or GM-CSF.

Claim 103: Immunogenic composition comprising at least one peptide consisting of an amino acid sequence of from 8 to 12 amino acids concatenated to each other in the isolated cancer associated cancer antigen of claim 89, and a pharmaceutically acceptable adjuvant.

Claim 104: The immunogenic composition of claim 103, wherein said adjuvant is a saponin, a cytokine, or GM-CSF.

Claim 105: The immunogenic composition of claim 102, wherein said composition comprises a plurality of peptides which complex with a specific MHC molecule.

Claim 106: Immunogenic composition which comprises at least one expression vector which encodes a peptide derived from the amino acid sequence encoded by SEQ ID NO: 15, 22 or 26.

Claim 107: The immunogenic composition of claim 106, wherein said at least one expression vector codes for a plurality of peptides.

Claim 108: Vaccine useful in treating a subject afflicted with a cancerous condition comprising the isolated eukaryotic cell line of claim 88 and a pharmacologically acceptable adjuvant.

Claim 109: The vaccine of claim 108, wherein said eukaryotic cell line has been rendered non-proliferative.

Claim 110: The vaccine of claim 109, wherein said eukaryotic cell line is a human cell line.

Claim 111: A composition of matter useful in treating a cancerous condition comprising a non-proliferative cell line having expressed on its surface a peptide derived from the amino acid sequence encoded by SEQ ID NO: 15, 22 or 26.

Claim 112: The composition of matter of claim 111, wherein said cell line is a human cell line.

Claim 113: A composition of matter useful in treating a cancerous condition, comprising (i) a peptide derived from the amino acid sequence encoded by SEQ ID NO: 15, 22 or 26, (ii) an MHC or HLA molecule, and (iii) a pharmaceutically acceptable carrier.

Claim 114: Isolated antibody which is specific for the cancer antigen of claim 89.

Claim 115: The isolated antibody of claim 114, wherein said antibody is a monoclonal antibody.

Claim 116: Method for screening for cancer in a sample, comprising contacting said sample with a nucleic acid molecule which hybridizes to all or part of the molecule encoded by SEQ ID NO: 15, 22 or 26 and determining hybridization as an indication of cancer cells in said sample.

Claim 117: A method for screening for cancer in a sample, comprising contacting said sample with the isolated antibody of claim 114, and determining binding of said antibody to a target as an indicator of cancer.

Claim 118: Method for diagnosing a cancerous condition in a subject, comprising contacting an immune reactive cell containing sample of said subject to a cell line transfected with the isolated nucleic acid molecule of claim 81, and determining interaction of said transfected cell line with said immunoreactive cell, said interaction being indicative of said cancer condition.

Claim 119: A method for determining regression, progression of onset of a cancerous condition comprising monitoring a sample from a patient with said cancerous condition for a parameter selected from the group consisting of (i) a protein encoded by SEQ ID NO: 15, 22 or 26, (ii) a peptide derived from said protein, (iii) cytolytic T cells specific for said peptide and an MHC molecule with which it non-covalently complexes, and (iv) antibodies specific for said CT protein, wherein amount of said parameter is indicative of progression or regression or onset of said cancerous condition.

Claim 120: The method of claim 119, wherein said sample is a body fluid or exudate.

Claim 121: The method of claim 119, wherein said sample is a tissue.

Claim 122: The method of claim 119, comprising contacting said sample with an antibody which specifically binds with said protein or peptide.

Claim 123: The method of claim 122, wherein said antibody is labelled with a radioactive label or an enzyme.

Claim 124: The method of claim 122, wherein said antibody is a monoclonal antibody.

Claim 125: The method of claim 119, comprising amplifying RNA which codes for said protein.

Claim 126: The method of claim 125, wherein said amplifying comprises carrying out polymerase chain reaction.

Claim 127: The method of claim 118, comprising contacting said sample with a nucleic acid molecule which specifically hybridizes to a nucleic acid molecule which codes for or expresses said protein.

Claim 128: The method of claim 127, wherein said nucleic acid molecule comprises SEQ ID NO: 17, 18, 20,21, 24, 25, 28 or 29.

Claim 129: The method of claim 119, comprising assaying said sample for shed protein.

Claim 130: The method of claim 119, comprising assaying said sample for antibodies specific for said protein, by contacting said sample with protein.

Claim 131: Method for diagnosing a cancerous condition comprising assaying a sample taken from a subject for an immunoreactive cell specific for a peptide derived from a protein encoded by SEQ ID NO: 15, 22 or 26, complexed to an MHC molecule, presence of said immunoreactive cell being indicative of said cancerous condition.

Claim 132: Composition comprising at least one peptide consisting of an amino acid sequence of from 8 to 25 amino acids concatenated to each other in the isolated cancer associated antigen of claim 89, and a pharmaceutically acceptable adjuvant.

Claim 133: The composition of claim 132, wherein said adjuvant is a saponin, a cytokine, or GM-CSF.

Claim 134: The composition of claim 132, comprising a plurality of MHC binding peptides.

Claim 135: Composition comprising an expression vector which encodes at least one peptide consisting of an amino acid sequence of from 8 to 25 amino acids concatenated to each other in the isolated cancer associated antigen of claim 89, and pharmaceutically acceptable adjuvant.

Claim 136: The composition of claim 135, wherein said expression vector encodes a plurality of peptides.

Claim 137: A method for screening for possible presence of a pathological condition, comprising assaying a sample from a patient believed to have a pathological condition for antibodies specific to at least one of the cancer associated antigens encoded by SEQ ID NO: 15, 22 or 26, presence of said antibodies being indicative of possible presence of said pathological condition.

Claim 138: The method of claim 137, wherein said pathological condition is cancer.

Claim 139: The method of claim 137, wherein said cancer is melanoma.

Claim 140: The method of claim 139, further comprising contacting said sample to a purified cancer associated antigen encoded by SEQ ID NO: 15, 22 or 26.

Claim 141: A method for screening for possible presence of a pathological condition in a subject, comprising assaying a sample taken from said subject for expression of a nucleic acid molecule, the nucleotide sequence of which comprises SEQ ID NO: 15, 22 or 26, expression of said nucleic acid molecule being indicative of possible presence of said pathological condition.

Claim 142: The method of claim 141, wherein said pathological condition is cancer.

Claim 143: The method of claim 141, comprising determining expression via polymerase chain reaction.

Claim 144: The method of claim 141, comprising determining expression by contacting said sample with at least one of SEQ ID NO: 17, 18, 20, 21, 24, 25, 28, or 29.

Claim 145: A method for determining regression, progression of onset of a cancerous condition comprising monitoring a sample from a patient with said cancerous condition for a parameter selected from the group consisting of (i) a cancer associated antigen encoded by SEQ ID NO: 15, 22 or 26 (ii) a peptide derived from said cancer associated antigen, (iii) cytolytic T cells specific for said peptide and an MHC molecule with which it non-covalently complexes, and (iv) antibodies specific for said cancer associated antigen, wherein amount of said parameter is indicative of progression or regression or onset of said cancerous condition.

Claim 146: The method of claim 145, wherein said sample is a body fluid or exudate.

Claim 147: The method of claim 145, wherein said sample is a tissue.

Claim 148: The method of claim 145, comprising contacting said sample with an antibody which specifically binds with said protein or peptide.

Claim 149: The method of claim 148, wherein said antibody is labelled with a radioactive label or an enzyme.

Claim 150: The method of claim 148, wherein said antibody is a monoclonal antibody.

Claim 151: The method of claim 145, comprising amplifying RNA which codes for said protein.

Claim 152: The method of claim 151, wherein said amplifying comprises carrying out polymerase chain reaction.

Claim 153: The method of claim 145, comprising contacting said sample with a nucleic acid molecule which specifically hybridizes to a nucleic acid molecule which codes for or expresses said protein.

Claim 154: The method of claim 145, comprising assaying said sample for shed cancer associated antigen.

Claim 155: The method of claim 145, comprising assaying said sample for antibodies specific for said cancer associated antigen, by contacting said sample with said cancer associated antigen.

Claim 156: Method for screening for a cancerous condition comprising assaying a sample taken from a subject for an immunoreactive cell specific for a peptide derived from a cancer associated antigen encoded by SEQ ID NO: 15, 22 or 26 complexed to an MHC molecule, presence of said immunoreactive cell being indicative of said cancerous condition.

Claim 157: An isolated nucleic acid molecule consisting of a nucleotide sequence defined by SEQ ID NO: 15, 22 or 26.

REMARKS

Entry of the foregoing amendment is requested.

Respectfully submitted,

FULBRIGHT & JAWORSKI, LLP

By _____
Norman D. Hanson
Reg. No. 30,946

666 Fifth Avenue

New York, New York 10103
(212) 318-3000

VIA EXPRESS MAIL
"Express Mail" mailing label Number EL227322248US
Date of Deposit June 22, 2000
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under CFR 1.10 on the date indicated above, and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231
FULBRIGHT & JAWORSKI L.L.P.
By: Denise Gurri

LUD 5615.1-JEL/NDH (1006411)

ISOLATED NUCLEIC ACID MOLECULES ENCODING CANCER ASSOCIATED ANTIGENS, THE ANTIGENS PER SE, AND USES THEREOF

RELATED APPLICATIONS

This application is a continuation in part of Serial No. 09/451,739 filed November 30, 1999, incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to antigens associated with cancer, the nucleic acid molecules encoding them, as well as the uses of these.

BACKGROUND AND PRIOR ART

It is fairly well established that many pathological conditions, such as infections, cancer, autoimmune disorders, etc., are characterized by the inappropriate expression of certain molecules. These molecules thus serve as "markers" for a particular pathological or abnormal condition. Apart from their use as diagnostic "targets", i.e., materials to be identified to diagnose these abnormal conditions, the molecules serve as reagents which can be used to generate diagnostic and/or therapeutic agents. A by no means limiting example of this is the use of cancer markers to produce antibodies specific to a particular marker. Yet another non-limiting example is the use of a peptide which complexes with an MHC molecule, to generate cytolytic T cells against abnormal cells.

Preparation of such materials, of course, presupposes a source of the reagents used to generate these. Purification from cells is one laborious, far from sure method of doing so. Another preferred method is the isolation of nucleic acid molecules which encode a particular marker, followed by the use of the isolated encoding molecule to express the desired molecule.

Two basic strategies have been employed for the detection of such antigens, in e.g., human tumors. These will be referred to as the genetic approach and the biochemical approach. The

genetic approach is exemplified by, e.g., dePlaen et al., Proc. Natl. Sci. USA 85: 2275 (1988), incorporated by reference. In this approach, several hundred pools of plasmids of a cDNA library obtained from a tumor are transfected into recipient cells, such as COS cells, or into antigen-negative variants of tumor cell lines which are tested for the expression of the specific antigen. The biochemical approach, exemplified by, e.g., O. Mandelboim, et al., Nature 369: 69 (1994) incorporated by reference, is based on acidic elution of peptides which have bound to MHC-class I molecules of tumor cells, followed by reversed-phase high performance liquid chromography (HPLC). Antigenic peptides are identified after they bind to empty MHC-class I molecules of mutant cell lines, defective in antigen processing, and induce specific reactions with cytotoxic T-lymphocytes. These reactions include induction of CTL proliferation, TNF release, and lysis of target cells, measurable in an MTT assay, or a ^{51}Cr release assay.

These two approaches to the molecular definition of antigens have the following disadvantages: first, they are enormously cumbersome, time-consuming and expensive; and second, they depend on the establishment of cytotoxic T cell lines (CTLs) with predefined specificity.

The problems inherent to the two known approaches for the identification and molecular definition of antigens is best demonstrated by the fact that both methods have, so far, succeeded in defining only very few new antigens in human tumors. See, e.g., van der Bruggen et al., Science 254: 1643-1647 (1991); Brichard et al., J. Exp. Med. 178: 489-495 (1993); Coulie, et al., J. Exp. Med. 180: 35-42 (1994); Kawakami, et al., Proc. Natl. Acad. Sci. USA 91: 3515-3519 (1994).

Further, the methodologies described rely on the availability of established, permanent cell lines of the cancer type under consideration. It is very difficult to establish cell lines from certain

cancer types, as is shown by, e.g., Oettgen, et al., Immunol. Allerg. Clin. North. Am. 10: 607-637 (1990). It is also known that some epithelial cell type cancers are poorly susceptible to CTLs in vitro, precluding routine analysis. These problems have stimulated the art to develop additional methodologies for identifying cancer associated antigens.

One key methodology is described by Sahin, et al., Proc. Natl. Acad. Sci. USA 92: 11810-11913 (1995), incorporated by reference. Also, see U.S. Patent No. 5,698,396, and Application Serial No. 08/479,328, filed on June 7, 1995 and January 3, 1996, respectively. All three of these references are incorporated by reference. To summarize, the method involves the expression of cDNA libraries in a prokaryotic host. (The libraries are secured from a tumor sample). The expressed libraries are then immunoscreened with absorbed and diluted sera, in order to detect those antigens which elicit high titer humoral responses. This methodology is known as the SEREX method ("Serological identification of antigens by Recombinant Expression Cloning"). The methodology has been employed to confirm expression of previously identified tumor associated antigens, as well as to detect new ones. See the above referenced patent applications and Sahin, et al., supra, as well as Crew, et al., EMBO J 144: 2333-2340 (1995).

This methodology has been applied to a range of tumor types, including those described by Sahin et al., supra, and Pfreundschuh, supra, as well as to esophageal cancer (Chen et al., Proc. Natl. Acad. Sci. USA 94: 1914-1918 (1997)); lung cancer (Güre et al., Cancer Res. 58: 1034-1041 (1998)); colon cancer (Serial No. 08/948, 705 filed October 10, 1997) incorporated by reference, and so forth. Among the antigens identified via SEREX are the SSX2 molecule (Sahin et al., Proc. Natl. Acad. Sci. USA 92: 11810-11813 (1995); Tureci et al., Cancer Res. 56: 4766-4772 (1996); NY-

ESO-1 Chen, et al., Proc. Natl. Acad. Sci. USA 94: 1914-1918 (1997); and SCP1 (Serial No. 08/892,705 filed July 15, 1997) incorporated by reference. Analysis of SEREX identified antigens has shown overlap between SEREX defined and CTL defined antigens. MAGE-1, tyrosinase, and NY-ESO-1 have all been shown to be recognized by patient antibodies as well as CTLs, showing that humoral and cell mediated responses do act in concert.

It is clear from this summary that identification of relevant antigens via SEREX is a desirable aim. The inventors have applied this methodology and have identified several new antigens associated with cancer, as detailed in the description which follows.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1

The SEREX methodology, as described by, e.g. Sahin, et al., Proc. Natl. Acad. Sci. USA 92: 11810-11813 (1995); Chen, et al., Proc. Natl. Acad. Sci. USA 94: 1914-1918 (1997), and U.S. Patent No. 5,698,396, all of which are incorporated by reference. In brief, total RNA was extracted from a sample of a cutaneous metastasis of a breast cancer patient (referred to as "BR11" hereafter), using standard CsCl guanidine thiocyanate gradient methodologies. A cDNA library was then prepared, using commercially available kits designed for this purpose. Following the SEREX methodology referred to supra, this cDNA expression library was amplified, and screened with either autologous BR11 serum which had been diluted to 1:200, or with allogeneic, pooled serum, obtained from 7 different breast cancer patients, which had been diluted to 1:1000. To carry out the screen, serum samples were first diluted to 1:10, and then preabsorbed with lysates of E. coli that had been

transfected with naked vector, and the serum samples were then diluted to the levels described supra. The final dilutions were incubated overnight at room temperature with nitrocellulose membranes containing phage plaques, at a density of 4-5000 plaque forming units ("pfus") per 130 mm plate.

Nitrocellulose filters were washed, and incubated with alkaline phosphatase conjugated, goat anti-human Fcγ secondary antibodies, and reactive phage plaques were visualized via incubation with 5-bromo-4-chloro-3-indolyl phosphate and nitroblue tetrazolium.

This procedure was also carried out on a normal testicular cDNA library, using a 1:200 serum dilution.

A total of $1.12x10^6$ pfus were screened in the breast cancer cDNA library, and 38 positive clones were identified. With respect to the testicular library, $4x10^5$ pfus were screened, and 28 positive clones were identified.

Additionally, $8x10^5$ pfus from the BR11 cDNA library were screened using the pooled serum described. Of these, 23 were positive.

The positive clones were subcloned, purified, and excised to forms suitable for insertion in plasmids. Following amplification of the plasmids, DNA inserts were evaluated via restriction mapping (EcoRI-XbaI), and clones which represented different cDNA inserts were sequenced using standard methodologies.

If sequences were identical to sequences found in GenBank, they were classified as known genes, while sequences which shared identity only with ESTs, or were identical to nothing in these data bases, were designated as unknown genes. Of the clones from the breast cancer library which were positive with autologous serum, 3 were unknown genes. Of the remaining 35, 15 were

identical to either NY-ESO-1, or SSX2, two known members of the CT antigen family described supra, while the remaining clones corresponded to 14 known genes. Of the testicular library, 12 of the clones were SSX2.

The NY-ESO-1 antigen was not found, probably because the commercial library that was used had been size fractionated to have an average length of 1.5 kilobases, which is larger than full length NY-ESO-1 cDNA which is about 750 base pairs long.

With respect to the screening carried out with pooled, allogeneic sera, four of the clones were NY-ESO-1. No other CT antigens were identified. With the exception of NY-ESO-1, all of the genes identified were expressed universally in normal tissue.

A full listing of the isolated genes, and their frequency of occurrence follows, in tables 1, 2 and 3. Two genes were found in both the BR11 and testicular libraries, i.e., poly (ADP-ribose) polymerase, and tumor suppression gene ING1. The poly (ADP-ribose) polymerase gene has also been found in colon cancer libraries screened via SEREX, as is disclosed by Scanlan, et al., Int. J. Cancer 76: 652-58 (1998) when the genes identified in the screening of the BR11 cDNA library by autologous and allogeneic sera were compared, NY-ESO-1 and human keratin.

Table 1. SEREX-defined genes identified by autologous screening of BR11 cDNA library

Gene group	No. of clones	Comments	Expression
CT genes	10	NY-ESO-1	tumor, testis
	5	SSX2	tumor, testis
Non-CT genes	5	Nuclear Receptor Co-Repressor	ubiquitous
	4	Poly(ADP-ribose) polymerase	ubiquitous
	2	Adenylosuccinatelyase	ubiquitous

2	cosmid 313 (human)	ESTs: muscle, brain, breast
1	CD 151 (transmembrane protein)	ubiquitous
1	Human HRY Gen	RT-PCR: multiple normal tissues
1	Alanyl-t-RNA-Synthetase	ubiquitous
1	NAD(+) ADP-Ribosyltransferase	ubiquitous
1	Human keratin 10	ESTs: multiple normal tissues
1	Human EGFR kinase substrate	ubiquitous
1	*ING 1* Tumor suppressor gene	RT-PCR: multiple normal tissues
1	Unknown gene, NCI_CGAP_Pr12 cDNA clone	ESTs: pancreas, liver, spleen, uterus
1	Unknown gene	ESTs: multiple normal tissues
1	Unknown gene	RT-PCR: multiple normal tissues

Table 2. SEREX-defined genes identified by allogeneic screening of BR11 cDNA library

Gene group	No. of clones	Comments	Expression
CT genes	4	NY-ESO-1	tumor, testis
Non-CT genes	6	zinc-finger helicase	ESTs: brain, fetal heart, total fetus
	4	Acetoacetyl-CoA-thiolase	ubiquitous
	3	KIAA0330 gene	ESTs: multiple normal tissues
	2	U1snRNP	ubiquitous
	1	Human aldolase A	ubiquitous
	1	Retinoblastoma binding protein 6	ESTs: tonsils, fetal brain, endothelial cells, brain
	1	α2-Macroglobulin receptor associated protein	ubiquitous
	1	Human Keratin 10	ESTs: multiple normal tissues

Table 3. SEREX-defined genes identified by screening of a testicular cDNA library with BR11 serum

Gene group	No. of clones	Comments	Expression

CT genes:	12	SSX2	tumor, testis
Non-CT genes:	3	Rho-associated coiled-coil forming protein	ubiquitous
	3	Poly(ADP-ribose) polymerase	ubiquitous
	3	Gene from HeLa cell, similar to TITIN	ubiquitous
	2	Gene from parathyroid tumor	RT-PCR: multiple normal tissues
	1	Transcription termination factor I-interacting peptide 21	ubiquitous
	1	Gene from fetal heart	ESTs: multiple normal tissues
	1	*ING 1* tumor suppressor gene	RT-PCR: multiple normal tissues
	1	KIAA0647 cDNA	ESTs: multiple normal tissues
	1	KIAA0667 cDNA	ESTs: multiple normal tissues

EXAMPLE 2

The mRNA expression pattern of the cDNAs identified in example 1, in both normal and malignant tissues, was studied. To do this, gene specific oligonucleotide primers were designed which would amplify cDNA segments 300-600 base pairs in length, using a primer melting temperature of 65-70° C. The primers used for amplifying MAGE-1,2,3 and 4, BAGE, NY-ESO-1, SCP1, and SSX1, 2, 3, 4 and 5 were known primers, or were based on published sequences. See Chen, et al. supra; Tureci, et al., Proc. Natl. Acad. Sci. USA 95: 5211-16 (1998). Gure, et al., Int. J. Cancer 72: 965-71 (1997); Chen, et al., Proc. Natl. Acad. Sci. USA 91: 1004-1008 (1994); Gaugler, et al., J. Exp. Med. 179: 921-930 (1994), dePlaen, et al., Immunogenetics 40: 360-369 (1994), all of which are incorporated by reference. RT-PCR was carried out for 35 amplification cycles, at an annealing temperature of 60° C. Using this RT-PCR assay, the breast cancer tumor

specimen was positive for a broad range of CT antigens, including MAGE-1,3 AND 4, BAGE, SSX2, NY-ESO-1 and CT7. The known CT antigens SCP-1, SSX1, 4 and 5 were not found to be expressed.

An additional set of experiments were carried out, in which the seroreactivity of patient sera against tumor antigens was tested. Specially, ELISAs were carried out, in accordance with Stockert, et al., J. Exp. Med. 187: 1349-1354 (1998), incorporated by reference, to determine if antibodies were present in the patient sera. Assays were run for MAGE-1, MAGE-3, NY-ESO-1, and SSX2. The ELISAs were positive for NY-ESO-1 and SSX2, but not the two MAGE antigens.

EXAMPLE 3

Two clones (one from the breast cancer cDNA library and one from the testicular library), were identified as a gene referred to as ING1, which is a tumor suppressor gene candidate. See Garkavtsev, et al., Nature 391: 295-8 (1998), incorporated by reference. The sequence found in the breast cancer library, differed from the known sequence of ING1 at six residues, i.e., positions 818, 836, 855, 861, 866 and 874. The sequence with the six variants is set forth at SEQ ID NO: 1. The sequence of wild type ING1 is set out at SEQ ID NO: 2.

To determine if any of these differences represented a mutation in tumors, a short, PCR fragment which contained the six positions referred to supra was amplified from a panel of allogeneic normal tissue, subcloned, amplified, and sequenced following standard methods.

The results indicated that the sequences in the allogeneic tissues were identical to what was found in tumors, ruling out the hypothesis that the sequence differences were a tumor associated

mutation. This conclusion was confirmed, using the testicular library clone, and using restriction analysis of ING1 cDNA taken from normal tissues. One must conclude, therefore, that the sequence information provided by Garkavtsev, et al., supra, is correct.

EXAMPLE 4

Additional experiments were carried out to determine whether genetic variations might exist in the 5′ portion of the ING1 gene, which might differ from the 5′ portion of the clone discussed supra (SEQ ID NO: 1). In a first group of experiments, attempts were made to obtain full length ING1 cDNA from both the breast tumor library, and the testicular library. SEQ ID NO: 1 was used as a probe of the library, using standard methods.

Four clones were isolated from the testicular library and none were isolated from the breast cancer library. The four clones, following sequencing, were found to derive from three transcript variants. The three variants were identical from position 586 down to their 3′ end, but differed in their 5′ regions, suggesting alternatively spliced variants, involving the same exon-intron junction. All three differed from the sequence of ING1 described by Garkavtsev, et al., in Nat. Genet. 14: 415-420 (1996). These three variants are set out as SEQ ID NOS: 1, 3 and 4.

All of the sequences were then analyzed. The ORFs of SEQ ID NOS: 2, 1 and 4 (SEQ ID NO: 2 is the originally disclosed , ING1 sequence), encode polypeptides of 294, 279 and 235 amino acids, of which 233 are encoded by the 3′ region common to the three sequences. These putative sequences are set out as SEQ ID NOS:19, 5, and 7. With respect to SEQ ID NO: 3, however, no translational initiation site could be identified in its 5′ region.

EXAMPLE 5

The data regarding SEQ ID NO: 3, described supra, suggested further experiments to find additional ORFs in the 5-end of variant transcripts of the molecule. In order to determine this, 5'-RACE -PCR was carried out using gene specific and adapted specific primers, together with commercially available products, and standard methodologies.

The primers used for these experiments were:

CACACAGGATCCATGTTGAGTCCTGCCAACGG

CGTGGTCGTGGTTGCTGGACGCG

(SEQ ID NOS: 9 and 10), for SEQ ID NO: 1;

CCCAGCGGCCCTGACGCTGTC

CGTGGTCGTGGTTGCTGGACGCG

(SEQ ID NOS: 11 and 12), for SEQ ID NO: 3; and

GGAAGAGATAAGGCCTAGGGAAG

CGTGGTCGTGGTTGCTGGACGCG

(SEQ ID NOS: 13 and 14), for SEQ ID NO: 4.

Cloning and sequencing of the products of RACE PCR showed that the variant sequence of SEQ ID NO: 4 was 5′ to SEQ ID NO: 3, and that full length cDNA for the variant SEQ ID NO: 3 contained an additional exon 609 nucleotides long, positioned between SEQ ID NO: 3 and the shared, 3′ sequence referred to supra. This exon did not include an ORF. The first available initiation site would be an initial methionine at amino acid 70 of SEQ ID NO: 1. Thus, if expressed,

SEQ ID NO: 3 would correspond to a molecule with a 681 base pair, untranslated 5′ end and a region encoding 210 amino acids (SEQ ID NO:6).

EXAMPLE 6

The presence of transcript variants with at least 3 different trancriptional initiation sites, and possibly different promoters, suggested that mRNA expression might be under different, tissue specific regulation.

To determine this, variant-specific primers were synthesized, and RT-PCR was carried out on a panel of tissues, using standard methods.

SEQ ID NO: 1 was found to be expressed universally in all of the normal breast, brain and testis tissues examined, in six breast cancer lines, and 8 melanoma cell lines, and in cultured melanocytes. SEQ ID NO: 3 was found to be expressed in four of the six breast cancer lines, normal testis, liver, kidney, colon and brain. SEQ ID NO: 4 was only found to be expressed by normal testis cells and weakly in brain cells.

EXAMPLE 7

A further set of experiments were carried out to determine if antibodies against ING1 were present in sera of normal and cancer patients. A phase plaque immuno assay of the type described supra was carried out, using clones of SEQ ID NO: 1 as target. Of 14 allogeneic sera taken from breast cancer patients, two were positive at 1:200 dilutions. All normal sera were negative.

EXAMPLE 8

The BR11 cDNA library described supra was then screened, using SEQ ID NO: 1 and standard methodologies. A 593 base pair cDNA was identified, which was different from any sequences in the data banks consulted. The sequence of this cDNA molecule is set out at SEQ ID NO: 8.

The cDNA molecule set forth as SEQ ID NO:1 was then used in Southern blotting experiments. In brief, genomic DNA was isolated from normal human tissue, digested with BamHI or Hind III, and then separated onto 0.7% agarose gel, blotted onto nitrocellulose filters, and hybridized using ^{32}P labelled SEQ ID NO: 1, at high stringency conditions (aqueous buffer, 65°C). The probes were permitted to hybridize overnight, and then exposed for autoradiography. Two hybridizing DNA species were identified, i.e., SEQ ID NOS: 1 and 8.

EXAMPLE 9

The cDNA molecule set forth in SEQ ID NO: 8 was then analyzed. 5′- RACE PCR was carried out using normal fetus cDNA. Full length cDNA for the molecule is 771 base pairs long, without the poly A tail. It shows strong homology to SEQ ID NO: 1, with the strongest homology in the 5′ two-thirds (76% identity over nucleotide 1-480); however, the longest ORF is only 129 base pairs, and would encode a poly peptide 42 amino acids long which was homologous to, but much shorter than, the expected expression product of SEQ ID NO: 1.

In addition to the coding region, SEQ ID NO: 8 contains 203 base pairs of 5′-untranslated region, and 439 base pairs of 3′-untranslated region.

RT-PCR assays were carried out, as described supra. All of the normal tissues tested, including brain, colon, testis, tissue and breast, were positive for expression of this gene. Eight melanoma cell lines were tested, of which seven showed varying levels of expression, and one showed no expression. Six breast cancer cell lines were tested, of which four showed various levels of expression, and two showed no expression.

EXAMPLE 10

An additional breast cancer cDNA library, referred to as "BR17-128", was screened, using autologous sera. A cDNA molecule was identified.

Analysis of the sequence suggested that it was incomplete at the 5′ end. To extend the sequence, a testicular cDNA library was screened with a nucleotide probe based upon the partial sequence identified in the breast cancer library. An additional 1200 base pairs were identified following these screenings. The 2011 base pairs of information are set forth in SEQ ID NO: 15.

The longest open reading frame is 1539 base pairs, corresponding to a protein of about 59.15 kilodaltons. The deduced sequence is set forth at SEQ ID NO: 16.

RT-PCR was then carried out using the following primers:

CACACAGGATCCATGCAGGCCCCGCACAAGGAG

CACACAAAGCTTCTAGGATTTGGCACAGCCAGAG

(SEQ ID NOS: 17 and 18)

Strong signals were observed in normal testis and breast tissue, and weak expression was observed in placenta.

No expression was found in normal brain, kidney, liver, colon, adrenal, fetal brain, lung, pancreas, prostate, thymus, uterus, and ovary tissue of tumor cell lines tested, 2 of the breast cancer lines were strongly positive and two were weakly positive. Of melanoma two of 8 were strongly positive, and 3 were weakly positive. Of lung cancer cell lines, 4 of 15 were strongly positive, and 3 were weakly positive.

When cancer tissue specimens were tested, 16 of 25 breast cancer samples were strongly positive, and 3 additional samples were weakly positive. Two of 36 melanoma samples were positive (one strong, one weak). All other cancer tissue samples were negative.

When Northern blotting was carried out, a high molecular weight smear was observed in testis, but in no other tissues tested.

EXAMPLE 11

Further experiments were carried out using the tumor sample referred to in example 10, supra. This sample was derived from a subcutaneous metastasis of a 60 year old female breast cancer patient. Total RNA was extracted, as described supra. Following the extraction, a cDNA library was constructed in λ-ZAP expression vectors, also as described supra. Screening was carried out, using the protocol set forth in example 1. A total of 7×10^5 pfus were screened. Fourteen reactive clones were identified, purified, and sequenced. The sequences were then compared to published sequences in GenBank and EST databases. These analyses indicated that the clones were derived from seven distinct genes, two of which were known, and five unknown. The two known

genes were "PBK-1" (three clones), and TI-227 (one clone). These are universally expressed genes, with the libraries referred to supra showing ESTs for these genes from many different tissues.

With respect to the remaining 10 clones, six were derived from the same gene, referred to hereafter as "NY-BR-1." Three cDNA sequences were found in the EST database which shared identity with the gene. Two of these (AI 951118 and AW 373574) were identified as being derived from a breast cancer library, while the third (AW 170035), was from a pooled tissue source.

EXAMPLE 12

The distribution of the new gene NY-BR-1 referred to supra was determined via RT-PCR. In brief, gene specific oligonucleotide NY-BR-1 primers were designed to amplify cDNA segments 300-600 base pairs in length, with primer melting temperatures estimated at 65-70°C. The RT-PCR was then carried out over 30 amplification cycles, using a thermal cycler, and an annealing temperature of 60°C. Products were analyzed via 1.5% gel electrophoresis, and ethidium bromide visualization. Fifteen normal tissues (adrenal gland, fetal brain, lung, mammary gland, pancreas, placenta, prostate, thymus, uterus, ovary, brain, kidney, liver, colon and testis) were assayed. The NY-BR-1 clone gave a strong signal in mammary gland and testis tissue, and a very faint signal in placenta. All other tissues were negative. The other clones were expressed universally, based upon comparison to information in the EST database library, and were not pursued further.

The expression pattern of NY-BR-1 in cancer samples was then tested, by carrying out RT-PCR, as described supra, on tumor samples.

In order to determine the expression pattern, primers:

caaagcagag cctcccgaga ag

(SEQ ID NO: 20) and

cctatgctgc tcttcgattc ttcc

(SEQ ID NO: 21) were used.

Of twenty-five breast cancer samples tested, twenty two were positive for NY-BR-1. Of these, seventeen gave strong signals, and five gave weak to modest signals.

An additional 82 non-mammary tumor samples were also analyzed, divided into 36 melanoma, 26 non small cell lung cancer, 6 colon cancer, 6 squamous cell carcinoma, 6 transitional cell carcinoma, and two leiyomyosarcomas. Only two melanoma samples were positive for NY-BR-1 expression.

The study was then extended to expression of NY-BR-1 in tissue culture. Cell lines derived from breast tumor, melanoma, and small cell lung cancer were studied. Four of six breast cancer cells were positive (two were very weak), four of eight melanoma (two very weak), and seven of fourteen small cell lung cancer lines (two very weak) were positive.

EXAMPLE 13

In order to determine the complete cDNA molecule for NY-BR-1, the sequences of the six clones referred to supra were compiled, to produce a nucleotide sequence 1464 base pairs long. Analysis of the open reading frame showed a continuous ORF throughout, indicating that the compiled sequence is not complete.

Comparison of the compiled sequence with the three EST library sequences referred to supra allowed for extension of the sequence. The EST entry AW170035 (446 base pairs long) overlapped the compiled sequence by 89 base pairs at its 5' end, permitting extension of the sequence by another 357 base pairs. A translational terminal codon was identified in this way, leading to a molecule with a 3'-untranslated region 333 base pairs long. The 5' end of the molecule was lacking, however, which led to the experiment described infra.

EXAMPLE 14

In order to determine the missing, 5' end of the clone described supra, a commercially available testis cDNA expression library was screened, using a PCR expression product of the type described supra as a probe. In brief, $5x10^4$ pfus per 150 mm plate were transferred to nitrocellulose membranes, which were then submerged in denaturation solution (1.5M NaCl and 0.5 M NaOH), transferred to neutralization solution (1.5 M NaCl and 0.5M Tris-HCl), and then rinsed with 0.2M Tris-HCl, and 2xSSC. Probes were labelled with ^{32}P and hybridization was carried out at high stringency conditions (i.e., 68°C, aqueous buffer). Any positive clones were subcloned, purified, and in vivo excised to plasmid PBK-CMV, as described supra.

One of the clones identified in this way included an additional 1346 base pairs at the 5' end; however, it was not a full length molecule. A 5'-RACE-PCR was carried out, using commercially available products. The PCR product was cloned into plasmid vector pGEMT and sequenced. The results indicated that cDNA sequence was extended 1292 base pairs further, but no translation initiation site could be determined, because no stop codons could be detected. It could be concluded,

however, that the cDNA of the NY-BR17 clone comprises at least 4026 nucleotides, which are presented as SEQ ID NO: 22. The molecule, as depicted, encodes a protein at least about 152.8 kDA in molecular weight. Structurally, there are 99 base pairs 5' to the presumed translation initiation site, and an untranslated segment 333 base pairs long at the 3' end. The predicted amino acid sequence of the coding region for SEQ ID NO: 22 is set out at SEQ. ID NO: 23.

SEQ ID NO: 23 was analyzed for motifs, using the known search programs PROSITE and Pfam. A bipartite nuclear localization signal motif was identified at amino acids 17-34, suggesting that the protein is a nuclear protein. Five tandem ankyrin repeats were identified, at amino acids 49-81, 82-114, 115-147, 148-180 and 181-213. A bZIP site (i.e. a DNA binding site followed by a leucine zipper motif) was found at amino acid positions 1077-1104, suggesting a transcription factor function. It was also observed that three repetitive elements were identified in between the ankyrin repeats and the bZIP DNA binding site. To elaborate, a repetitive element 117 nucleotides long is trandemly repeated 3 times, between amino acids 459-815. The second repetitive sequence, consisting of 11 amino acids, repeats 7 times between amino acids 224 and 300. The third repetitive element, 34 amino acids long, is repeated twice, between amino acids 301-368.

EXAMPLE 15

The six clones described supra were compared, and analysis revealed that they were derived from two different splice variants. Specifically, two clones, referred to as "BR17-8" and "BR 17-44a", contain one more exon, of 111 base pairs (nucleotides 3015-3125 of SEQ ID NO: 22), which encodes amino acids 973-1009 of SEQ ID NO: 23, than do clones BR 17-1a, BR17-35b and BR17-

44b. The shortest of the six clones, BR17-128, starts 3' to the additional exons. The key structural elements referred to supra were present in both splice variants, suggesting that there was no difference in biological function.

The expression pattern of the two splice variants was assessed via PT-PCR, using primers which spanned the 111 base pair exon referred to supra.

The primers used were:

aatgggaaca agagctctgc ag

(SEQ ID NO: 24) and

gggtcatctg aagttcagca ttc

(SEQ ID NO: 25)

Both variants were expressed strongly in normal testis and breast. The longer variant was dominant in testis, and the shorter variant in breast cells. When breast cancer cells were tested, co-typing of the variant was observed, (7 strongly, 2 weakly positive, and 1 negative), with the shorter variant being the predominant form consistently.

EXAMPLE 16

The frequency of antibody response against NY-BR-1 in breast cancer patients was tested. To do this, a recombinant protein consisting of amino acids 993-1188 of SEQ ID NO: 23 was prepared. (This is the protein encoded by clone BR 17-128, referred to supra). A total of 140 serum samples were taken from breast cancer patients, as were 60 normal serum samples. These were analyzed via Western blotting, using standard methods.

Four of the cancer sera samples were positive, including a sample from patient BR17. All normal sera were negative.

An additional set of experiments was then carried out to determine if sera recognized the portion of NY-BR-1 protein with repetitive elements. To do this, a different recombinant protein, consisting of amino acids 405-1000 was made, and tested in Western blot assays. None of the four antibody positive sera reacted with this protein indicating that an antibody epitope is located in the non-repetitive, carboxy terminal end of the molecule.

EXAMPLE 17

The screening of the testicular cDNA library referred to supra resulted, inter alia, in the identification of a cDNA molecule that was homologous to NY-BR-1. The molecule is 3673 base pairs in length, excluding the poly A tail. This corresponded to nucleotides 1-3481 of SEQ ID NO: 22, and showed 62% homology thereto. No sequence identity to sequences in libraries was noted. ORF analysis identified an ORF from nucleotide 641 through the end of the sequence, with 54% homology to the protein sequence of SEQ. ID NO: 23. The ATG initiation codon of this sequence is 292 base pairs further 3' to the presumed initiation codon of NY-BR-1, and is preceded by 640 untranslated base pairs at its 5' end. This 640 base pair sequence includes scattered stop codons. The nucleotide sequence and deduced amino acid sequence are presented as SEQ ID NOS: 26 and 27, respectively.

RT-PCR analysis was carried out in the same way as is described supra, using primers:

tct catagat gctggtgctg atc

(SEQ ID NO: 28) and

cccagacatt gaattttggc agac

(SEQ ID NO: 29).

Tissue restricted mRNA expression was found. The expression pattern differed from that of SEQ ID NO: 22. In brief, of six normal tissues examined, strong signals were found in brain and testis only. There was no or weak expression in normal breast tissues, and kidney, liver and colon tissues were negative. Eight of ten 10 breast cancer specimens tested supra were positive for SEQ. ID NO:

26. Six samples were positive for both SEQ. ID NO: 22 and 26, one for SEQ. ID NO: 22 only, two for the SEQ. ID NO: 26 only, and one was negative for both.

The foregoing examples describe the isolation of a nucleic acid molecule which encodes a cancer associated antigen. "Associated" is used herein because while it is clear that the relevant molecule was expressed by several types of cancer, other cancers, not screened herein, may also express the antigen.

The invention relates to nucleic acid molecules which encode the antigens encoded by, e.g., SEQ ID NOS: 1, 3, 8, 15, 22 and 26 as well as the antigens encoded thereby, such as the proteins with the amino acid sequences of SEQ ID NOS: 5, 6, 7, 16, 23 and 27. It is to be understood that all sequences which encode the recited antigen are a part of the invention.

Also a part of the invention are expression vectors which incorporate the nucleic acid molecules of the invention, in operable linkage (i.e., "operably linked") to a promoter. Construction of such vectors, such as viral (e.g., adenovirus or Vaccinia virus) or attenuated viral vectors is well within the skill of the art, as is the transformation or transfection of cells, to produce eukaryotic cell lines, or prokaryotic cell strains which encode the molecule of interest. Exemplary of the host cells which can be employed in this fashion are COS cells, CHO cells, yeast cells, insect cells (e.g., Spodoptera frugiperda), NIH 3T3 cells, and so forth. Prokaryotic cells, such as E. coli and other bacteria may also be used. Any of these cells can also be transformed or transfected with further nucleic acid molecules, such as those encoding cytokines, e.g., interleukins such as IL-2, 4, 6, or 12 or HLA or MHC molecules.

Also a part of the invention are the antigens described herein, both in original form and in any different post translational modified forms. The molecules are large enough to be antigenic without any posttranslational modification, and hence are useful as immunogens, when combined with an adjuvant (or without it), in both precursor and post-translationally modified forms. Antibodies produced using these antigens, both poly and monoclonal, are also a part of the invention as well as hybridomas which make monoclonal antibodies to the antigens. The whole protein can be used therapeutically, or in portions, as discussed infra. Also a part of the invention are antibodies against this antigen, be these polyclonal, monoclonal, reactive fragments, such as Fab, $(F(ab)_2'$ and other fragments, as well as chimeras, humanized antibodies, recombinantly produced antibodies, and so forth.

As is clear from the disclosure, one may use the proteins and nucleic acid molecules of the invention diagnostically. The SEREX methodology discussed herein is premised on an immune response to a pathology associated antigen. Hence, one may assay for the relevant pathology via, e.g., testing a body fluid sample of a subject, such as serum, for reactivity with the antigen per se. Reactivity would be deemed indicative of possible presence of the pathology. So, too, could one assay for the expression of any of the antigens via any of the standard nucleic acid hybridization assays which are well known to the art, and need not be elaborated upon herein. One could assay for antibodies against the subject molecules, using standard immunoassays as well.

Analysis of SEQ ID NO: 1, 3, 4, 8, 15, 22 and 26 will show that there are 5′ and 3′ non-coding regions presented therein. The invention relates to those isolated nucleic acid molecules

which contain at least the coding segment, and which may contain any or all of the non-coding 5′ and 3′ portions.

Also a part of the invention are portions of the relevant nucleic acid molecules which can be used, for example, as oligonucleotide primers and/or probes, such as one or more of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 17, 18,20, 21, 24, 25, 28, and 29 as well as amplification products like nucleic acid molecules comprising at least nucleotides 305-748 of SEQ ID NO: 1, or amplification products described in the examples, including those in examples 12, 14, etc.

As was discussed supra, study of other members of the "CT" family reveals that these are also processed to peptides which provoke lysis by cytolytic T cells. There has been a great deal of work on motifs for various MHC or HLA molecules, which is applicable here. Hence, a further aspect of the invention is a therapeutic method, wherein one or more peptides derived from the antigens of the invention which bind to an HLA molecule on the surface of a patient's tumor cells are administered to the patient, in an amount sufficient for the peptides to bind to the MHC/HLA molecules, and provoke lysis by T cells. Any combination of peptides may be used. These peptides, which may be used alone or in combination, as well as the entire protein or immunoreactive portions thereof, may be administered to a subject in need thereof, using any of the standard types of administration, such as intravenous, intradermal, subcutaneous, oral, rectal, and transdermal administration. Standard pharmaceutical carriers, adjuvants, such as saponins, GM-CSF, and interleukins and so forth may also be used. Further, these peptides and proteins may be formulated into vaccines with the listed material, as may dendritic cells, or other cells which present relevant MHC/peptide complexes.

Similarly, the invention contemplates therapies wherein nucleic acid molecules which encode the proteins of the invention, one or more or peptides which are derived from these proteins are incorporated into a vector, such as a Vaccinia or adenovirus based vector, to render it transfectable into eukaryotic cells, such as human cells. Similarly, nucleic acid molecules which encode one or more of the peptides may be incorporated into these vectors, which are then the major constituent of nucleic acid bases therapies.

Any of these assays can also be used in progression/regression studies. One can monitor the course of abnormality involving expression of these antigens simply by monitoring levels of the protein, its expression, antibodies against it and so forth using any or all of the methods set forth supra.

It should be clear that these methodologies may also be used to track the efficacy of a therapeutic regime. Essentially, one can take a baseline value for a protein of interest using any of the assays discussed supra, administer a given therapeutic agent, and then monitor levels of the protein thereafter, observing changes in antigen levels as indicia of the efficacy of the regime.

As was indicated supra, the invention involves, inter alia, the recognition of an "integrated" immune response to the molecules of the invention. One ramification of this is the ability to monitor the course of cancer therapy. In this method, which is a part of the invention, a subject in need of the therapy receives a vaccination of a type described herein. Such a vaccination results, e.g., in a T cell response against cells presenting HLA/peptide complexes on their cells. The response also includes an antibody response, possibly a result of the release of antibody provoking proteins via the lysis of cells by the T cells. Hence, one can monitor the effect of a vaccine, by monitoring an antibody

response. As is indicated, supra, an increase in antibody titer may be taken as an indicia of progress with a vaccine, and vice versa. Hence, a further aspect of the invention is a method for monitoring efficacy of a vaccine, following administration thereof, by determining levels of antibodies in the subject which are specific for the vaccine itself, or a large molecule of which the vaccine is a part.

The identification of the subject proteins as being implicated in pathological conditions such as cancer also suggests a number of therapeutic approaches in addition to those discussed supra. The experiments set forth supra establish that antibodies are produced in response to expression of the protein. Hence, a further embodiment of the invention is the treatment of conditions which are characterized by aberrant or abnormal levels of one or more of the proteins, via administration of antibodies, such as humanized antibodies, antibody fragments, and so forth. These may be tagged or labelled with appropriate cystostatic or cytotoxic reagents.

T cells may also be administered. It is to be noted that the T cells may be elicited in vitro using immune responsive cells such as dendritic cells, lymphocytes, or any other immune responsive cells, and then reperfused into the subject being treated.

Note that the generation of T cells and/or antibodies can also be accomplished by administering cells, preferably treated to be rendered non-proliferative, which present relevant T cell or B cell epitopes for response, such as the epitopes discussed supra.

The therapeutic approaches may also include antisense therapies, wherein an antisense molecule, preferably from 10 to 100 nucleotides in length, is administered to the subject either "neat" or in a carrier, such as a liposome, to facilitate incorporation into a cell, followed by inhibition of expression of the protein. Such antisense sequences may also be incorporated into appropriate

vaccines, such as in viral vectors (e.g., Vaccinia), bacterial constructs, such as variants of the known BCG vaccine, and so forth.

Other features and applications of the invention will be clear to the skilled artisan, and need not be set forth herein. The terms and expression which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expression of excluding any equivalents of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

We claim:

1. Isolated nucleic acid molecule which encodes a cancer associated antigen, whose amino acid sequence is identical to the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1, 3, 4, 8, 15 or 19.

2. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 1.

3. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 3.

4. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 4.

5. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 8.

6. The isolated nucleic acid molecule of claim 1, comprising the nucleotide sequence of SEQ ID NO: 15.

7. The isolated nucleic acid molecules of claim 1, comprising the nucleotide sequence of SEQ ID NO: 19.

8. Expression vector comprising the isolated nucleic acid molecule of claim 1, operably linked to a promoter.

9. Eukaryotic cell line or prokaryotic cell strain, transformed or transfected with the expression vector of claim 8.

10. Isolated cancer associated antigen comprising all or part of the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15 or 19.

11. Eukaryotic cell line or prokaryotic cell strain, transformed or transfected with the isolated nucleic acid molecule of claim 1.

12. The eukaryotic cell line or prokaryotic cell strain of claim 11, wherein said cell line is also transfected with a nucleic acid molecule coding for a cytokine.

13. The eukaryotic cell line or prokaryotic cell strain of claim 12, wherein said cell line is further transfected by a nucleic acid molecule coding for an MHC molecule.

14. The eukaryotic cell line or prokaryotic cell strain of claim 12, wherein said cytokine is an interleukin.

15. The eukaryotic cell line or prokaryotic cell strain of claim 14, wherein said interleukin is IL-2, IL-4 or IL-12.

16. The eukaryotic cell line or prokaryotic cell strain of claim 11, wherein said cell line has been rendered non-proliferative.

17. The eukaryotic cell line of claim 11, wherein said cell line is a fibroblast cell line.

18. Expression vector comprising a mutated or attenuated virus and the isolated nucleic acid molecule of claim 1.

19. The expression vector of claim 18, wherein said virus is adenovirus or vaccinia virus.

20. The expression vector of claim 19, wherein said virus is vaccinia virus.

21. The expression vector of claim 19, wherein said virus is adenovirus.

22. Expression system useful in transfecting a cell, comprising (i) a first vector containing a nucleic acid molecule which codes for the isolated cancer associated antigen of claim 11 and (ii) a second vector selected from the group consisting of (a) a vector containing a nucleic acid molecule which codes for an MHC or HLA molecule which presents an antigen derived from said cancer associated antigen and (b) a vector containing a nucleic acid molecule which codes for an interleukin.

23. Immunogenic composition comprising the isolated cancer antigen of claim 10, and a pharmaceutically acceptable adjuvant.

24. The immunogenic composition of claim 23, wherein said adjuvant is a cytokine, a saponin, or GM-CSF.

25. Immunogenic composition comprising at least one peptide consisting of an amino acid sequence of from 8 to 12 amino acids concatenated to each other in the isolated cancer associated cancer antigen of claim 11, and a pharmaceutically acceptable adjuvant.

26. The immunogenic composition of claim 25, wherein said adjuvant is a saponin, a cytokine, or GM-CSF.

27. The immunogenic composition of claim 24, wherein said composition comprises a plurality of peptides which complex with a specific MHC molecule.

28. Immunogenic composition which comprises at least one expression vector which encodes a peptide derived from the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15 or 19.

29. The immunogenic composition of claim 28, wherein said at least one expression vector codes for a plurality of peptides.

30. Vaccine useful in treating a subject afflicted with a cancerous condition comprising the isolated eukaryotic cell line of claim 11 and a pharmacologically acceptable adjuvant.

31. The vaccine of claim 30, wherein said eukaryotic cell line has been rendered non-proliferative.

32. The vaccine of claim 31, wherein said eukaryotic cell line is a human cell line.

33. A composition of matter useful in treating a cancerous condition comprising a non-proliferative cell line having expressed on its surface a peptide derived from the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15 or 19.

34. The composition of matter of claim 33, wherein said cell line is a human cell line.

35. A composition of matter useful in treating a cancerous condition, comprising (i) a peptide derived from the amino acid sequence encoded by SEQ ID NO: 1, 3, 4, 8, 15 or 19, (ii) an MHC or HLA molecule, and (iii) a pharmaceutically acceptable carrier.

36. Isolated antibody which is specific for the cancer antigen of claim 10.

37. The isolated antibody of claim 36, wherein said antibody is a monoclonal antibody.

38. Method for screening for cancer in a sample, comprising contacting said sample with a nucleic acid molecule which hybridizes to all or part of the molecule encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15 or 19 and determining hybridization as an indication of cancer cells in said sample.

39. A method for screening for cancer in a sample, comprising contacting said sample with the isolated antibody of claim 36, and determining binding of said antibody to a target as an indicator of cancer.

40. Method for diagnosing a cancerous condition in a subject, comprising contacting an immune reactive cell containing sample of said subject to a cell line transfected with the isolated nucleic acid molecule of claim 1, and determining interaction of said transfected cell line with said immunoreactive cell, said interaction being indicative of said cancer condition.

41. A method for determining regression, progression of onset of a cancerous condition comprising monitoring a sample from a patient with said cancerous condition for a parameter selected from the group consisting of (i) a protein encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15 or 19, (ii) a peptide derived from said protein, (iii) cytolytic T cells specific for said peptide and an MHC molecule with which it non-covalently complexes, and (iv) antibodies specific for said CT protein, wherein amount of said parameter is indicative of progression or regression or onset of said cancerous condition.

42. The method of claim 41, wherein said sample is a body fluid or exudate.

43. The method of claim 41, wherein said sample is a tissue.

44. The method of claim 41, comprising contacting said sample with an antibody which specifically binds with said protein or peptide.

45. The method of claim 44, wherein said antibody is labelled with a radioactive label or an enzyme.

46. The method of claim 44, wherein said antibody is a monoclonal antibody.

47. The method of claim 41, comprising amplifying RNA which codes for said protein.

48. The method of claim 47, wherein said amplifying comprises carrying out polymerase chain reaction.

49. The method of claim 40, comprising contacting said sample with a nucleic acid molecule which specifically hybridizes to a nucleic acid molecule which codes for or expresses said protein.

50. The method of claim 49, wherein said nucleic acid molecule comprises SEQ ID NO: 9, 10, 11, 12, 13, 14, 17 or 18.

51. The method of claim 41, comprising assaying said sample for shed protein.

52. The method of claim 41, comprising assaying said sample for antibodies specific for said protein, by contacting said sample with protein.

53. Method for diagnosing a cancerous condition comprising assaying a sample taken from a subject for an immunoreactive cell specific for a peptide derived from a protein encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15 or 19, complexed to an MHC molecule, presence of said immunoreactive cell being indicative of said cancerous condition.

54. Composition comprising at least one peptide consisting of an amino acid sequence of from 8 to 25 amino acids concatenated to each other in the isolated cancer associated antigen of claim 10, and a pharmaceutically acceptable adjuvant.

55. The composition of claim 54, wherein said adjuvant is a saponin, a cytokine, or GM-CSF.

56. The composition of claim 54, comprising a plurality of MHC binding peptides.

57. Composition comprising an expression vector which encodes at least one peptide consisting of an amino acid sequence of from 8 to 25 amino acids concatenated to each other in the isolated cancer associated antigen of claim 10, and pharmaceutically acceptable adjuvant.

58. The composition of claim 57, wherein said expression vector encodes a plurality of peptides.

59. A method for screening for possible presence of a pathological condition, comprising assaying a sample from a patient believed to have a pathological condition for antibodies specific to at least one of the cancer associated antigens encoded by SEQ ID NOS: 1, 2, 3, 4, 8, 15 or 19, presence of said antibodies being indicative of possible presence of said pathological condition.

60. The method of claim 59, wherein said pathological condition is cancer.

61. The method of claim 59, wherein said cancer is melanoma.

62. The method of claim 61, further comprising contacting said sample to purified cancer associated antigen encoded by SEQ ID NO: 1, 3, 4, 8, or 15.

63. A method for screening for possible presence of a pathological condition in a subject, comprising assaying a sample taken from said subject for expression of a nucleic acid molecule, the nucleotide sequence of which comprises SEQ ID NO: 1, 2, 3, 4, 8, 15 or 19, expression of said nucleic acid molecule being indicative of possible presence of said pathological condition.

64. The method of claim 63, wherein said pathological condition is cancer.

65. The method of claim 63, comprising determining expression via polymerase chain reaction.

66. The method of claim 63, comprising determining expression by contacting said sample with at least one of SEQ ID NO: 9, 10, 11, 12, 13 or 14.

67. A method for determining regression, progression of onset of a cancerous condition comprising monitoring a sample from a patient with said cancerous condition for a parameter selected from the group consisting of (i) a cancer associated antigen encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15 or 19 (ii) a peptide derived from said cancer associated antigen, (iii) cytolytic T cells specific for said peptide and an MHC molecule with which it non-covalently complexes, and (iv) antibodies specific for said cancer associated antigen, wherein amount of said parameter is indicative of progression or regression or onset of said cancerous condition.

68. The method of claim 67, wherein said sample is a body fluid or exudate.

69. The method of claim 67, wherein said sample is a tissue.

70. The method of claim 67, comprising contacting said sample with an antibody which specifically binds with said protein or peptide.

71. The method of claim 70, wherein said antibody is labelled with a radioactive label or an enzyme.

72. The method of claim 70, wherein said antibody is a monoclonal antibody.

73. The method of claim 67, comprising amplifying RNA which codes for said protein.

74. The method of claim 73, wherein said amplifying comprises carrying out polymerase chain reaction.

75. The method of claim 67, comprising contacting said sample with a nucleic acid molecule which specifically hybridizes to a nucleic acid molecule which codes for or expresses said protein.

76. The method of claim 67, comprising assaying said sample for shed cancer associated antigen.

77. The method of claim 67, comprising assaying said sample for antibodies specific for said cancer associated antigen, by contacting said sample with said cancer associated antigen.

78. Method for screening for a cancerous condition comprising assaying a sample taken from a subject for an immunoreactive cell specific for a peptide derived from a cancer associated antigen encoded by SEQ ID NO: 1, 2, 3, 4, 8, 15 or 19 complexed to an MHC molecule, presence of said immunoreactive cell being indicative of said cancerous condition.

79. An isolated nucleic acid molecule consisting of a nucleotide sequence defined by SEQ ID NO: 1, 2, 3, 8, 15 or 19.

80. Isolated nucleic acid molecule the complimentary sequence of which hydridizes, under stringent conditions, to the nucleotide sequence set forth in SEQ ID NO: 4, 5, 8, 15 or 19.

ABSTRACT OF THE DISCLOSURE

The invention relates to newly identified cancer associated antigens. It has been discovered that each of these molecules provokes antibodies when expressed by a subject. The ramifications of this observation are also a part of this invention.

COMBINED DECLARATION AND POWER OF ATTORNEY	Attorney Docket No. LUD 5615.1 (10006411)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "**ISOLATED NUCLEIC ACID MOLECULES ENCODING CANCER ASSOCIATED ANTIGENS, THE ANTIGENS PER SE, AND USES THEREOF**", the specification of which

(check one) ☒ is attached hereto.

☐ was filed on
and was amended on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below>

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s) or § 365(b) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior U.S. or PCT international application in the manner provided by the first paragraph of Title 35, U.S.C. § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
09/451,739	November 30, 1999	Pending
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or an patent issued thereon.

Power of Attorney

I hereby appoint the following attorneys to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Peter F. Felfe, Reg. No. 20,297; John E. Lynch, Reg. No. 20,940; Norman D. Hanson, Reg. No. 30,946; John A. Bauer, Reg. No. 32,554; James Zubok, Reg. No. 38,671; Mary Ann Schofield, Reg. No. 36,669; James R. Crawford, Reg. No. 39,155, Eric Sinn, Reg. No 40,177, and C. Andrew Im, Reg. No. 40,657 my attorneys with full power of substitution and revocation. Address all telephone calls to **NORMAN D. HANSON, Esq.**, at (212) 318-3000 Address all correspondence to:

FULBRIGHT & JAWORSKI L.L.P., 666 Fifth Avenue, New York, New York 10103

are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Sixth Inventor	Inventor's Signature	Date
JAGER, Dirk		

Residence	Citizenship
1275 York Avenue, New York, New York 10021, USA	German

Post Office Address
1275 York Avenue, New York, New York 10021, USA

Full Name of Sole or First Inventor	Inventor's Signature	Date
STOCKERT, Elizabeth		

Residence	Citizenship
1275 York Avenue, New York, New York 10021, USA	Austrian

Post Office Address
1275 York Avenue, New York, New York 10021, USA

Post Office Address		
SCANLAN, Matthew		

Residence	Citizenship
1275 York Avenue, New York, New York 10021, USA	US

Post Office Address
1275 York Avenue, New York, New York 10021, USA

Full Name of Fifth Inventor	Inventor's Signature	Date
GURE, Ali		

Residence	Citizenship
1275 York Avenue, New York, New York 10021, USA	Turkish

Post Office Address
1275 York Avenue, New York, New York 10021, USA

Full Name of Second Inventor	Inventor's Signature	Date
JAGER, Elke		

Residence	Citizenship
Steinbacher Hohl 2-28, 60488 Frankfurt am Main Germany	German

Post Office Address
Steinbacher Hohl 2-28, 60488 Frankfurt am Main Germany

Post Office Address		
KNUTH, Alexander		

Residence	Citizenship
Steinbacher Hohl 2-28, 60488 Frankfurt am Main Germany	German

Post Office Address
Steinbacher Hohl 2-28, 60488 Frankfurt am Main Germany

Post Office Address	
OLD, Lloyd	

Residence	Citizenship
605 Third Avenue, New York, New York 10158, USA	USA

Post Office Address
605 Third Avenue, New York, New York 10158, USA

Post Office Address	
CHEN, Yao-tseng	

Residence	Citizenship
525 E. 68th Street, New York, New York 10021, USA	Taiwanese

Post Office Address
525 E. 68th Street, New York, New York 10021, USA

<110> Jager, Dirk
Scanlan, Matthew
Gure, Ali
Jager, Elke
Knuth, Alexander
Old, Lloyd
Chen, Yao-tseng

<120> Isolated Nucleic Acid Molecules Encoding Cancer Associated Antigens, the Antigens per se, and Uses Thereof

<130> LUD 5615.1

<140>

<141>

<150> 09/451,739

<151> 1999-11-30

<160> 28

<210> 1
<211> 1533
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 235
<400> 1
ggttttccac gttggacaag tgcggctcgg cggccagcgg agcgcgcccc ttcccgctgc 60

ccgctccgct cctctcttct acccagccca gtgggcgagt gggcagcggc ggccgcggcg 120

ctgggccctc tcccgccggt gtgtgcgcgc tcgtacgcgc ggcccccggc gccagccccg 180

ccgcctgaga gggggcctgc gccgccggcc ggggcgtgcg cccgggagcc accgncaccg 240

cggcccgcgc cctcaggcgc tggggtcccc gcggacccgg aggcggcgga cgggctcggc 300

agatgtagcc gccgggccga agcaggagcc ggcgggggggg cgccgggaga gcgagggctt 360

tgcattttgc agtgctattt tttgaggggg gcggagggtg gaggaagtcg gaaagccgcg 420

ccgagtcgcc ggggacctcc ggggtgaacc atgttgagtc ctgccaacgg ggagcagctc 480

cacctggtga actatgtgga ggactacctg gactccatcg agtccctgcc tttcgacttg 540

cagagaaatg tctcgctgat gcgggagatc gacgcgaaat accaagagat cctgaaggag 600

ctagacgagt gctacgagcg cttcagtcgc gagacagacg gggcgcagaa gcggcggatg 660

ctgcactgtg tgcagcgcgc gctgatccgc agccaggagc tgggcgacga gaagatccag 720

atcgtgagcc agatggtgga gctggtggag aaccgcacgc ggcaggtgga cagccacgtg 780

gagctgttcg aggcgcagca ggagctgggc gacacagcgg gcaacagcgg caaggctggc 840

gcggacaggc ccaaaggcga ggcggcagcg caggctgaca agcccaacag caagcgctca 900

cggcggcagc gcaacaacga gaaccgtgag aacgcgtcca gcaaccacga ccacgacgac 960

ggcgcctcgg gcacacccaa ggagaagaag gccaagacct ccaagaagaa gaagcgctcc 1020

aaggccaagg cggagcgaga ggcgtcccct gccgacctcc ccatcgaccc caacgaaccc 1080

acgtactgtc tgtgcaacca ggtctcctat ggggagatga tcggctgcga caacgacgag 1140

tgccccatcg agtggttcca cttctcgtgc gtggggctca atcataaacc caagggcaag 1200

tggtactgtc ccaagtgccg gggggagaac gagaagacca tggacaaagc cctggagaaa 1260

tccaaaaaag agagggctta caacaggtag tttgtggaca ggcgcctggt gtgaggagga 1320

caaaataaac cgtgtattta ttacattgct gcctttgttg aggtgcaagg agtgtaaaat 1380

gtatattttt aaagaatgtt agaaaaggaa ccattccttt catagggatg gcagtgattc 1440

tgtttgcctt ttgttttcat tggtacacgt gtaacaagaa agtggtctgt ggatcagcat 1500

tttagaaact acaaatatag gtttgattca aca 1533

<210> 2
<211> 1143
<212> DNA
<213> Homo sapiens
<220>
<400> 2
gagtaacccg ataatatgcc gttgtccggc acggcgacga gaattcccag atatagcagt 60

agcagtgatc ccgggcctgt ggctcggggc cggggctgca gttcggaccg cctcccgcga 120

cccgcggggg ctcggagaca gtttcaggcc gcatctttgc tgacccgagg gtggggccgc 180

gcgtggccgt ggaaacagat cctgaaggag ctagacgagt gctacgagcg cttcagtcgc 240

gagacagacg gggcgcagaa gcggcggatg ctgcactgtg tgcagcgcgc gctgatccgc 300

agccaggagc tgggcgacga gaagatccag atcgtgagcc agatggtgga gctggtggag 360

aaccgcacgc ggcaggtgga cagccacgtg gagctgttcg aggcgcagca ggagctgggc 420

gacacagtgg gcaacagcgg caaggttggc gcggacaggc ccaatggcga tgcggtagcg 480

cagtctgaca agcccaacag caagcgctca cggcggcagc gcaacaacga gaaccgtgag 540

aacgcgtcca gcaaccacga ccacgacgac ggcgcctcgg gcacacccaa ggagaagaag 600

gccaagacct ccaagaagaa gaagcgctcc aaggccaagg cggagcgaga ggcgtcccct 660

gccgacctcc ccatcgaccc caacgaaccc acgtactgtc tgtgcaacca ggtctcctat 720

ggggagatga tcggctgcga caacgacgag tgccccatcg agtggttcca cttctcgtgc 780

gtggggctca atcataaacc caagggcaag tggtactgtc ccaagtgccg gggggagaac 840

gagaagacca tggacaaagc cctggagaaa tccaaaaaag agagggctta caacaggtag 900

tttgtggaca ggcgcctggt gtgaggagga caaaataaac cgtgtattta ttacattgct 960

gcctttgttg aggtgcaagg agtgtaaaat gtatattttt aaagaatgtt agaaaaggaa 1020

ccattccttt catagggatg gcagtgattc tgtttgcctt ttgttttcat tggtacacgt 1080

gtaacaagaa agtggtctgt ggatcagcat tttagaaact acaaatatag gtttgattca 1140

aca 1143

<210> 3
<211> 742
<212> DNA

<213> Homo sapiens
<220>
<400> 3
cgccgtccac accccagcgg ccctgacgct gtcccctccg cgaccctcgc ctctggaaaa 60

agtgacaggc aaggccacgc ccccgcgagg gccggcctcg agcccgcagc ccccagggcc 120

tgggacgaga tcctgaagga gctagacgag tgctacgagc gcttcagtcg cgagacagac 180

ggggcgcaga agcggcggat gctgcactgt gtgcagcgcg cgctgatccg cagccaggag 240

ctgggcgacg agaagatcca gatcgtgagc cagatggtgg agctggtgga gaaccgcacg 300

cggcaggtgg acagccacgt ggagctgttc gaggcgcagc aggagctggg cgacacagcg 360

ggcaacagcg gcaaggctgg cgcggacagg cccaaaggcg aggcggcagc gcaggctgac 420

aagcccaaca gcaagcgctc acggcggcag cgcaacaacg agaaccgtga gaacgcgtcc 480

agcaaccacg accacgacga cggcgcctcg ggcacaccca aggagaagaa ggccaagacc 540

tccaagaaga agaagcgctc caaggccaag gcggagcgag aggcgtcccc tgccgacctc 600

cccatcgacc ccaacgaacc cacgtactgt ctgtgcaacc aggtctccta tggggagatg 660

atcggctgcg acaacgacga gtgccccatc gagtggttcc acttctcgtg cgtggggctc 720

aatcataaac ccaagggcaa gt 742

<210> 4
<211> 857
<212> DNA
<213> Homo sapiens
<220>
<400> 4
cctccgagaa cggtgtccat ggcacagggc gggaagagat aaggcctagg gaaggcgccc 60

ctcgggccta tccacctctt ctggggctcg gcactaggaa gcagcttccc tctcaggccc 120

ctttgtctcc aagccgttcc aaactgagta ccgggagacg acacaaaggg agggcggtga 180

cggatggcgc aggcgcggga gccgcctagg ctgctgggag tggtggtccg gccgcggaat 240

ggagatcctg aaggagctag acgagtgcta cgagcgcttc agtcgcgaga cagacggggc 300

gcagaagcgg cggatgctgc actgtgtgca gcgcgcgctg atccgcagcc aggagctggg 360

cgacgagaag atccagatcg tgagccagat ggtggagctg gtggagaacc gcacgcggca 420

ggtggacagc cacgtggagc tgttcgaggc gcagcaggag ctgggcgaca cagcgggcaa 480

cagcggcaag gctggcgcgg acaggcccaa aggcgaggcg gcagcgcagg ctgacaagcc 540

caacagcaag cgctcacggc ggcagcgcaa caacgagaac cgtgagaacg cgtccagcaa 600

ccacgaccac gacgacggcg cctcgggcac acccaaggag aagaaggcca agacctccaa 660

gaagaagaag cgctccaagg ccaaggcgga gcgagaggcg tcccctgccg acctccccat 720

cgaccccaac gaacccacgt actgtctgtg caaccaggtc tcctatgggg agatgatcgg 780

ctgcgacaac gacgagtgcc ccatcgagtg gttccacttc tcgtgcgtgg ggctcaatca 840

taaacccaag ggcaagt 857

<210> 5
<211> 279
<212> PRT
<213> Homo sapiens
<220>
<400> 5

```
Met Leu Ser Pro Ala Asn Gly Glu Gln Leu His Leu Val Asn Tyr Val
1               5                  10                  15

Glu Asp Tyr Leu Asp Ser Ile Glu Ser Leu Pro Phe Asp Leu Gln Arg
            20                  25                  30

Asn Val Ser Leu Met Arg Glu Ile Asp Ala Lys Tyr Gln Glu Ile Leu
        35                  40                  45

Lys Glu Leu Asp Glu Cys Tyr Glu Arg Phe Ser Arg Glu Thr Asp Gly
    50                  55                  60

Ala Gln Lys Arg Arg Met Leu His Cys Val Gln Arg Ala Leu Ile Arg
65                  70                  75                  80

Ser Gln Glu Leu Gly Asp Glu Lys Ile Gln Ile Val Ser Gln Met Val
                85                  90                  95

Glu Leu Val Glu Asn Arg Thr Arg Gln Val Asp Ser His Val Glu Leu
            100                 105                 110

Phe Glu Ala Gln Gln Glu Leu Gly Asp Thr Val Gly Asn Ser Gly Lys
        115                 120                 125

Val Gly Ala Asp Arg Pro Asn Gly Asp Ala Val Ala Gln Ser Asp Lys
    130                 135                 140

Pro Asn Ser Lys Arg Ser Arg Arg Gln Arg Asn Asn Glu Asn Arg Glu
145                 150                 155                 160

Asn Ala Ser Ser Asn His Asp His Asp Asp Gly Ala Ser Gly Thr Pro
                165                 170                 175

Lys Glu Lys Lys Ala Lys Thr Ser Lys Lys Lys Lys Arg Ser Lys Ala
            180                 185                 190

Lys Ala Glu Arg Glu Ala Ser Pro Ala Asp Leu Pro Ile Asp Pro Asn
        195                 200                 205

Glu Pro Thr Tyr Cys Leu Cys Asn Gln Val Ser Tyr Gly Glu Met Ile
    210                 215                 220

Gly Cys Asp Asn Asp Glu Cys Pro Ile Glu Trp Phe His Phe Ser Cys
225                 230                 235                 240

Val Gly Leu Asn His Lys Pro Lys Gly Lys Trp Tyr Cys Pro Lys Cys
                245                 250                 255

Arg Gly Glu Asn Glu Lys Thr Met Asp Lys Ala Leu Glu Lys Ser Lys
            260                 265                 270

Lys Glu Arg Ala Tyr Asn Arg
        275
```

<210> 6
<211> 210
<212> PRT
<213> Homo sapiens
<220>
<400> 6

```
Met Leu His Cys Val Gln Arg Ala Leu Ile Arg Ser Gln Glu Leu Gly
1               5                   10                  15

Asp Glu Lys Ile Gln Ile Val Ser Gln Met Val Glu Leu Val Glu Asn
            20                  25                  30

Arg Thr Arg Gln Val Asp Ser His Val Glu Leu Phe Glu Ala Gln Gln
        35                  40                  45

Glu Leu Gly Asp Thr Val Gly Asn Ser Gly Lys Val Gly Ala Asp Arg
    50                  55                  60

Pro Asn Gly Asp Ala Val Ala Gln Ser Asp Lys Pro Asn Ser Lys Arg
65                  70                  75                  80

Ser Arg Arg Gln Arg Asn Asn Glu Asn Arg Glu Asn Ala Ser Ser Asn
                85                  90                  95

His Asp His Asp Asp Gly Ala Ser Gly Thr Pro Lys Glu Lys Lys Ala
            100                 105                 110

Lys Thr Ser Lys Lys Lys Lys Arg Ser Lys Ala Lys Ala Glu Arg Glu
        115                 120                 125

Ala Ser Pro Ala Asp Leu Pro Ile Asp Pro Asn Glu Pro Thr Tyr Cys
    130                 135                 140

Leu Cys Asn Gln Val Ser Tyr Gly Glu Met Ile Gly Cys Asp Asn Asp
145                 150                 155                 160

Glu Cys Pro Ile Glu Trp Phe His Phe Ser Cys Val Gly Leu Asn His
                165                 170                 175

Lys Pro Lys Gly Lys Trp Tyr Cys Pro Lys Cys Arg Gly Glu Asn Glu
            180                 185                 190

Lys Thr Met Asp Lys Ala Leu Glu Lys Ser Lys Lys Glu Arg Ala Tyr
        195                 200                 205

Asn Arg
    210
```

<210> 7
<211> 235
<212> PRT
<213> Homo sapiens
<220>
<400> 7

```
Met Glu Ile Leu Lys Glu Leu Asp Glu Cys Tyr Glu Arg Phe Ser Arg
1               5                   10                  15

Glu Thr Asp Gly Ala Gln Lys Arg Arg Met Leu His Cys Val Gln Arg
            20                  25                  30

Ala Leu Ile Arg Ser Gln Glu Leu Gly Asp Glu Lys Ile Gln Ile Val
        35                  40                  45

Ser Gln Met Val Glu Leu Val Glu Asn Arg Thr Arg Gln Val Asp Ser
    50                  55                  60

His Val Glu Leu Phe Glu Ala Gln Gln Glu Leu Gly Asp Thr Val Gly
65                  70                  75                  80

Asn Ser Gly Lys Val Gly Ala Asp Arg Pro Asn Gly Asp Ala Val Ala
                85                  90                  95
```

```
Gln Ser Asp Lys Pro Asn Ser Lys Arg Ser Arg Arg Gln Arg Asn Asn
            100                 105                 110

Glu Asn Arg Glu Asn Ala Ser Ser Asn His Asp His Asp Asp Gly Ala
        115                 120                 125

Ser Gly Thr Pro Lys Glu Lys Lys Ala Lys Thr Ser Lys Lys Lys Lys
    130                 135                 140

Arg Ser Lys Ala Lys Ala Glu Arg Glu Ala Ser Pro Ala Asp Leu Pro
145                 150                 155                 160

Ile Asp Pro Asn Glu Pro Thr Tyr Cys Leu Cys Asn Gln Val Ser Tyr
                165                 170                 175

Gly Glu Met Ile Gly Cys Asp Asn Asp Glu Cys Pro Ile Glu Trp Phe
            180                 185                 190

His Phe Ser Cys Val Gly Leu Asn His Lys Pro Lys Gly Lys Trp Tyr
        195                 200                 205

Cys Pro Lys Cys Arg Gly Glu Asn Glu Lys Thr Met Asp Lys Ala Leu
    210                 215                 220

Glu Lys Ser Lys Lys Glu Arg Ala Tyr Asn Arg
225                 230                 235
```

<210> 8
<211> 772
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 695,714
<400> 8

```
aaagcgttct cggcggcagc gcaacaacta gaaccgtgag aacgcgtcca gcaaccgcga   60

cccacgacga cgtcacctcg ggcacgccca aggagaagaa agcccagacc tctaagaaga  120

agcagggctc catggccaag gcgtagcggc aggcgtcccc cgcagacctc cccatcgacc  180

ccagcgagcc ctcctactgg gagatgatcc gctgcgacaa cgaatgcccc atcgagtggt  240

tccgcttctc gtgtgtgagt ctcaaccata aaccaaagcg caagtggtac tgttccagat  300

gccggggaaa gaacgatggg caaagccctt gagaagtcca gaaaaaaaac agggcttata  360

acaggtagtt tggggacatg cgtctaatag tgaggagaac aaaataagcc agtgtgttga  420

ttacattgcc acctttgctg aggtgcagga agtgtaaaat gtatattttt aaagaatgtt  480

gttagaggcc gggcgcggtg gctcacgcct gtaatcccag cactttggga ggccgaggcg  540

gtcggatcac gaggtcagga gatcgagacc atcctggcta acacggtgaa accccgtctc  600

tactaaaaat tcaaaaaaaa aattagctgg gcgtggtggc gggcgcctgt agtcccagct  660

attcgggagg ctgaggcagg agaatggcnt gaacctggga ggtggagctt gcantgagcc  720

aaggtcgcgc cactgcactc cagcctgggc gacagagcga gactccatct ta          772
```

<210> 9
<211> 32
<212> DNA
<213> Homo sapiens

<220>
<400> 9
cacacaggat ccatgttgag tcctgccaac gg 32

<210> 10
<211> 23
<212> DNA
<213> Homo sapiens
<220>
<400> 10
cgtggtcgtg gttgctggac gcg 23

<210> 11
<211> 21
<212> DNA
<213> Homo sapiens
<220>
<400> 11
cccagcggcc ctgacgctgt c 21

<210> 12
<211> 23
<212> DNA
<213> Homo sapiens
<220>
<400> 12
cgtggtcgtg gttgctggac gcg 23

<210> 13
<211> 23
<212> DNA
<213> Homo sapiens
<220>
<400> 13
ggaagagata aggcctaggg aag 23

<210> 14
<211> 23
<212> DNA
<213> Homo sapiens
<220>
<400> 14
cgtggtcgtg gttgctggac gcg 23

<210> 15
<211> 2030
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 1628, 1752, 1758, 1769, 1789, 1873, 1908, 1915, 1933, 1970, 1976, 2022
<400> 15
ctcgtgccgt taaagatggt cttctgaagg ctaactgcgg aatgaaagtt tctattccaa 60

ctaaagcctt agaattgatg gacatgcaaa ctttcaaagc agagcctccc gagaagccat 120

ctgccttcga gcctgccatt gaaatgcaaa agtctgttcc aaataaagcc ttggaattga 180

agaatgaaca aacattgaga gcagatgaga tactcccatc agaatccaaa caaaaggact 240

atgaagaaag ttcttgggat tctgagagtc tctgtgagac tgtttcacag aaggatgtgt 300

gtttacccaa ggctacacat caaaaagaaa tagataaaat aaatggaaaa ttagaagagt 360

ctcctgataa tgatggtttt ctgaaggctc cctgcagaat gaaagtttct attccaacta 420

aagccttaga attgatggac atgcaaactt tcaaagcaga gcctcccgag aagccatctg 480

ccttcgagcc tgccattgaa atgcaaaagt ctgttccaaa taaagccttg gaattgaaga 540

atgaacaaac attgagagca gatcagatgt tcccttcaga atcaaaacaa aagaaggttg 600

aagaaaattc ttgggattct gagagtctcc gtgagactgt ttcacagaag gatgtgtgtg 660

tacccaaggc tacacatcaa aaagaaatgg ataaaataag tggaaaatta gaagattcaa 720

ctagcctatc aaaaatcttg gatacagttc attcttgtga aagagcaagg gaacttcaaa 780

aagatcactg tgaacaacgt acaggaaaaa tggaacaaat gaaaaagaag ttttgtgtac 840

tgaaaaagaa actgtcagaa gcaaaagaaa taaaatcaca gttagagaac caaaaagtta 900

aatgggaaca agagctctgc agtgtgagat tgactttaaa ccaagaagaa gagaagagaa 960

gaaatgccga tatattaaat gaaaaaatta gggaagaatt aggaagaatc gaagagcagc 1020

ataggaaaga gttagaagtg aaacaacaac ttgaacaggc tctcagaata caagatatag 1080

aattgaagag tgtagaaagt aatttgaatc aggtttctca cactcatgaa aatgaaaatt 1140

atctcttaca tgaaaattgc atgttgaaaa aggaaattgc catgctaaaa ctggaaatag 1200

ccacactgaa acaccaatac caggaaaagg aaaataaata ctttgaggac attaagattt 1260

taaaagaaaa gaatgctgaa cttcagatga ccctaaaact gaaagaggaa tcattaacta 1320

aaagggcatc tcaatatagt gggcagctta aagttctgat agctgagaac acaatgctca 1380

cttctaaatt gaaggaaaaa caagacaaag aaatactaga ggcagaaatt gaatcacacc 1440

atcctagact ggcttctgct gtacaagacc atgatcaaat tgtgacatca agaaaaagtc 1500

aagaacctgc tttccacatt gcaggagatg cttgtttgca aagaaaaatg aatgttgatg 1560

tgagtagtac cgatatataa caatgaggtg ctccatcaac cactttctga agctcaaagg 1620

aaatccanaa gcctaaaaat taatctcaat tatgcaggag atgctctaag agaaaataca 1680

ttggtttcag gaacatgcac aaagagacca acgtgaaaca cagtgtcaaa tgaaggaagc 1740

tgaacacatg tntcaaancg aacaagatna tgtgaacaaa cacactganc agcaggagtc 1800

tctagatcag aaattatttc aactacaaag caaaaatatg tggcttcaac agcaattagt 1860

tcatgcacat aangaaagct gacaacaaaa gcaagataac aattgatntt cattntcttg 1920

agaggaaaat gcncatcatc ttctaaaaga gaaaaatgag gagatatttn attacnataa 1980

ccatttaaaa aacccgtata tttcaatatg gaaaaaaaaa anaaaaaaaa 2030

<210> 16
<211> 528
<212> PRT
<213> Homo sapiens
<220>
<400> 16
Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln
1 5 10 15

```
Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala
            20                  25                  30

Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn
        35                  40                  45

Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln
    50                  55                  60

Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr
65                  70                  75                  80

Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His Gln Lys Glu
                85                  90                  95

Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp Gly
            100                 105                 110

Phe Leu Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys Ala
        115                 120                 125

Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys
    130                 135                 140

Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn
145                 150                 155                 160

Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln Met
                165                 170                 175

Phe Pro Ser Glu Ser Lys Gln Lys Lys Val Glu Glu Asn Ser Trp Asp
            180                 185                 190

Ser Glu Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val Pro
        195                 200                 205

Lys Ala Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu Glu
    210                 215                 220

Asp Ser Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys Glu
225                 230                 235                 240

Arg Ala Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly Lys
                260                 265                 270

Met Glu Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu Ser
        275                 280                 285

Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys Trp
    290                 295                 300

Glu Gln Glu Leu Cys Ser Val Arg Leu Thr Leu Asn Gln Glu Glu Glu
305                 310                 315                 320

Lys Arg Arg Asn Ala Asp Ile Leu Asn Glu Lys Ile Arg Glu Glu Leu
                325                 330                 335

Gly Arg Ile Glu Glu Gln His Arg Lys Glu Leu Glu Val Lys Gln Gln
            340                 345                 350

Leu Glu Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val Glu
        355                 360                 365

Ser Asn Leu Asn Gln Val Ser His Thr His Glu Asn Glu Asn Tyr Leu
    370                 375                 380

Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys Leu
```

385 390 395 400

Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys Tyr
405 410 415

Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln Met
420 425 430

Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln Tyr
435 440 445

Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr Ser
450 455 460

Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile Glu
465 470 475 480

Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln Ile
485 490 495

Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly Asp
500 505 510

Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Asp Ile
515 520 525

<210> 17
<211> 33
<212> DNA
<213> Homo sapiens
<220>
<400> 17
cacacaggat ccatgcaggc cccgcacaag gag 33

<210> 18
<211> 34
<212> DNA
<213> Homo sapiens
<220>
<400> 18
cacacaaagc ttctaggatt tggcacagcc agag 34

<210> 19
<211> 294
<212> PRT
<213> Homo sapiens
<220>
<400> 19
Met Pro Leu Cys Thr Ala Thr Arg Ile Pro Arg Tyr Ser Ser Ser Ser
1 5 10 15

Asp Pro Gly Pro Val Ala Arg Gly Arg Gly Cys Ser Ser Asp Arg Leu
20 25 30

Pro Arg Pro Ala Gly Pro Ala Arg Arg Gln Phe Gln Ala Ala Ser Leu
35 40 45

Leu Thr Arg Gly Trp Gly Arg Ala Trp Pro Trp Lys Gln Ile Leu Lys
50 55 60

Glu Leu Asp Glu Cys Tyr Glu Arg Phe Ser Arg Glu Thr Asp Gly Ala
65 70 75 80

Gln Lys Arg Arg Met Leu His Cys Val Gln Arg Ala Leu Ile Arg Ser

```
                85                  90                  95

Gln Glu Leu Gly Asp Glu Lys Ile Gln Ile Val Ser Gln Met Val Glu
            100                 105                 110

Leu Val Glu Asn Arg Thr Arg Gln Val Asp Ser His Val Glu Leu Phe
        115                 120                 125

Glu Ala Gln Gln Glu Leu Gly Asp Thr Val Gly Asn Ser Gly Lys Val
    130                 135                 140

Gly Ala Asp Arg Pro Asn Gly Asp Ala Val Ala Gln Ser Asp Lys Pro
145                 150                 155                 160

Asn Ser Lys Arg Ser Arg Arg Gln Arg Asn Asn Glu Asn Arg Glu Asn
                165                 170                 175

Ala Ser Ser Asn His Asp His Asp Asp Gly Ala Ser Gly Thr Pro Lys
            180                 185                 190

Glu Lys Lys Ala Lys Thr Ser Lys Lys Lys Lys Arg Ser Lys Ala Lys
        195                 200                 205

Ala Glu Arg Glu Ala Ser Pro Ala Asp Leu Pro Ile Asp Pro Asn Glu
    210                 215                 220

Pro Thr Tyr Cys Leu Cys Asn Gln Val Ser Tyr Gly Glu Met Ile Gly
225                 230                 235                 240

Cys Asp Asn Asp Glu Cys Pro Ile Glu Trp Phe His Phe Ser Cys Val
                245                 250                 255

Gly Leu Asn His Lys Pro Lys Gly Lys Trp Tyr Cys Pro Lys Cys Arg
            260                 265                 270

Gly Glu Asn Glu Lys Thr Met Asp Lys Ala Leu Glu Lys Ser Lys Lys
        275                 280                 285

Glu Arg Ala Tyr Asn Arg
    290             294


<210> 20
<211> 22
<212> DNA
<213> Homo sapiens
<220>
<400> 20
caagcagag cctcccgaga ag 22

<210> 21
<211> 24
<212> DNA
<213> Homo sapiens
<220>
<400> 21
cctatgctgc tcttcgattc ttcc 24


<210> 22
<211> 4095
<212> DNA
<213> Homo sapiens
<220>
<400> 22
ctagtctata cagcaacgac cctacatcgt cactctgggg tcttagaaag tccataaagc   60
```

tgcctcccgg gacaagtccg aagctggaga gatgacaaag ggaagaagac atcaacctta 120

atatacaaga gcccagaaga gactgctcta actgggcctg gtcaatggcc tgaggaagta 180

gtaacatttc ggtagacaga agtgccagct gacgtccttg tggcgaacac ggacacctct 240

gatgaaggct tacaatgcca caggaggctt tgcaaatatt tgatagattc ggtgccgata 300

taaatctcgt gatgtgtatg caacatggct tccattatgc gtttatagtg gattttgtca 360

gtggtggcaa actgctgtcc atggtgcagt atcgaagtgc caacaaggct gcctcacacc 420

acttttacta ccataacgaa agaagtgagc aattgtggaa ttttgctgat aaaaatgcaa 480

atgcgaatgc gttaataagt taaatgcaca ccctcatgct gctgtatgtc tggatcatca 540

gagatagttg catgcttctt agcaaaatgt gacgtctttg tgcagatata gtggagtaac 600

tgcagaacat atgctgttac tgtggatttc tcacattcat aacaaattat gaatatatac 660

gaaaattatc aaaaatcatc aaataccaat cagaaggaac tctgcaggaa acctgatgag 720

gctgcaccct ggcggaaaga cacctgacac gctgaaagct ggtggaaaaa cacctgatga 780

ggctgcaccc tggtggaaag acacctgaca ggctgaaagc tggtggaaaa acacctgatg 840

aggctgcatc ttggtggagg aacatctgac aaattcaatg ttggagaaag gacatctgga 900

aagttcgaac gtcagcagaa aaacacctag gaaattacga tcctgcaaaa aaacatctga 960

gaaatttacg ggccagcaaa ggaagaccta gaagatcgca gggagaaaaa gaagacacac 1020

ctagggaaat atgagtcccg aaaagaaaca ctgagaaatt acgtgggcag aaaaggaaga 1080

cctaggaaga cgcatgggag aaaaagaaac cctgtaaaga tggatgcgtg caagagtaac 1140

atctaataaa ctaaagtttt gaaaaaggaa atctaagatg ttgcatgtcc acaaaagaat 1200

catctacaaa gcaagtgcca tgatcagagg tcccatcaga tccaaacaag ggaagatgaa 1260

gaatattctt tgattctcgg gtctctttga agttctgcaa gattcaagtg gtatacctga 1320

gtctatatat aaaaagtaat gagataaata agaagtagaa agcctcctaa aagccatctg 1380

ccttcaagcc gccattgaaa gcaaaactct ttccaaataa gcctttgaat gaagaatgaa 1440

caaacattga agcagatccg tgttcccacc gaatccaaac aaaggactat aagaaaattc 1500

ttgggattct agagtctctg gagactgttt acagaaggat tgtgtttacc aaggctacac 1560

atcaaaaaga atagataaaa aaatggaaaa tagaagagtc cctaataaag tggtcttctg 1620

aaggctacct cggaatgaaa tttctattcc actaaagcct agaattgaag acatgcaaac 1680

tttcaaagcg agcctccggg aagccatctg cttcgagcct ccactgaaat caaaagtctg 1740

tcccaaataa gccttggaat gaaaaatgaa aaacatggag gcagatgaga actcccatca 1800

gaatccaaac aaaggactat aagaaaattc tgggatactg gagtctctgt agactgtttc 1860

acagaaggat tgtgtttacc aaggctgcgc tcaaaaagaa tagataaaat aatggaaaat 1920

tagaagggtc cctgttaaag tggtcttctg aggctaactg ggaatgaaag ttctattcca 1980

actaaagcct agaattgatg acatgcaaac ttcaaagcag gcctcccgag agccatctgc 2040

cttcgagcct ccattgaaat caaaagtctg tccaaataaa ccttggaatt aagaatgaac 2100

aaacattgag gcagatgaga actcccatca aatccaaaca aaggactatg agaaagttct 2160

tgggattctg gagtctctgt agactgtttc cagaaggatg gtgtttaccc aggctacaca 2220

tcaaaaagaa tagataaaat aatggaaaat agaagagtct ctgataatga ggttttctga 2280

aggctccctg agaatgaaag ttctattcca ctaaagcctt gaattgatgg catgcaaact 2340

ttcaaagcag gcctcccgag agccatctgc ttcgagcctg cattgaaatg aaaagtctgt 2400

tccaaataaa ccttggaatt aagaatgaac aacattgaga cagatcagat ttcccttcag 2460

aatcaaaaca aagaaggttg agaaaattct gggattctga agtctccgtg gactgtttca 2520

cagaaggatg gtgtgtaccc aggctacaca caaaaagaaa ggataaaata gtggaaaatt 2580

agaagattca ctagcctatc aaaatcttgg tacagttcat cttgtgaaag gcaagggaac 2640

ttcaaaaaga cactgtgaac acgtacagga aaatggaaca atgaaaaaga gttttgtgta 2700

ctgaaaaaga actgtcagaa caaaagaaat aaatcacagt agagaaccaa aagttaaatg 2760

ggaacaagag tctgcagtgt agattgactt aaaccaagaa aagagaagag agaaatgccg 2820

atatattaaa gaaaaaatta ggaagaatta gaagaatcga gagcagcata gaaagagtta 2880

gaagtgaaac acaacttgaa aggctctcag atacaagata agaattgaag gtgtagaaag 2940

taatttgaat aggtttctca actcatgaaa tgaaaattat tcttacatga aattgcatgt 3000

tgaaaaagga attgccatgc aaaactggaa tagccacact aaacaccaat ccaggaaaag 3060

gaaaataaat ctttgaggac ttaagatttt aaagaaaaga tgctgaactt agatgaccct 3120

aaaactgaaa aggaatcatt actaaaaggg atctcaatat gtgggcagct aaagttctga 3180

tagctgagaa acaatgctca ttctaaattg aggaaaaaca gacaaagaaa actagaggca 3240

gaaattgaat acaccatcct gactggcttc gctgtacaag ccatgatcaa ttgtgacatc 3300

aagaaaaagt aagaacctgc ttccacattg aggagatgct gtttgcaaag aaaatgaatg 3360

ttgatgtgag agtacgatat taacaatgag tgctccatca ccactttctg agctcaaagg 3420

aaatccaaaa cctaaaaatt atctcaatta gcaggagatg tctaagagaa atacattggt 3480

ttcagaacat cacaaagaga caacgtgaaa acagtgtcaa tgaaggaagc gaacacatgt 3540

atcaaaacga caagataatg gaacaaacac ctgaacagca gagtctctag tcagaaatta 3600

tttcaactac aagcaaaaat tgtggcttca cagcaattag tcatgcacat agaaagctga 3660

caacaaaagc agataacaat gatattcatt tcttgagagg aaatgcaaca catctcctaa 3700

aagagaaaaa gaggagatat taattacaat accatttaaa aaccgtatat tcaatatgaa 3760

aaagagaaag agaaacagaa actcatgaga acaagcagta gaaacttctt tggagaaaca 3820

acagaccaga ctttactcac actcatgcta gaggccagtc tagcatcacc tatgttgaaa 3880

atcttaccaa agtctgtgtc acagaatact attttagaag aaaattcatg tttcttcctg 3940

aagcctacag cataaaataa agtgtgaaga ttacttgttc cgaattgcat aagctgcaca 4000

ggattcccat taccctgatg tgcagcagac tcattcaatc aaccagaatc cgctctgcac 4060

tccagcctag tgacagagtg gactccacct ggaaa 4095

<210> 23
<211> 1341
<212> PRT
<213> Homo sapiens
<220>
<400> 23

```
Met Thr Lys Arg Lys Lys Thr Ile Asn Leu Asn Ile Gln Asp Ala Gln
1               5                  10                  15

Lys Arg Thr Ala Leu His Trp Ala Cys Val Asn Gly His Glu Glu Val
            20                  25                  30

Val Thr Phe Leu Val Asp Arg Lys Cys Gln Leu Asp Val Leu Asp Gly
        35                  40                  45

Glu His Arg Thr Pro Leu Met Lys Ala Leu Gln Cys His Gln Glu Ala
    50                  55                  60

Cys Ala Asn Ile Leu Ile Asp Ser Gly Ala Asp Ile Asn Leu Val Asp
65                  70                  75                  80

Val Tyr Gly Asn Met Ala Leu His Tyr Ala Val Tyr Ser Glu Ile Leu
                85                  90                  95

Ser Val Val Ala Lys Leu Leu Ser His Gly Ala Val Ile Glu Val His
            100                 105                 110

Asn Lys Ala Ser Leu Thr Pro Leu Leu Leu Ser Ile Thr Lys Arg Ser
        115                 120                 125

Glu Gln Ile Val Glu Phe Leu Leu Ile Lys Asn Ala Asn Ala Asn Ala
    130                 135                 140

Val Asn Lys Tyr Lys Cys Thr Ala Leu Met Leu Ala Val Cys His Gly
145                 150                 155                 160

Ser Ser Glu Ile Val Gly Met Leu Leu Gln Gln Asn Val Asp Val Phe
                165                 170                 175

Ala Ala Asp Ile Cys Gly Val Thr Ala Glu His Tyr Ala Val Thr Cys
            180                 185                 190

Gly Phe His His Ile His Glu Gln Ile Met Glu Tyr Ile Arg Lys Leu
        195                 200                 205

Ser Lys Asn His Gln Asn Thr Asn Pro Glu Gly Thr Ser Ala Gly Thr
    210                 215                 220

Pro Asp Glu Ala Ala Pro Leu Ala Glu Arg Thr Pro Asp Thr Ala Glu
225                 230                 235                 240

Ser Leu Val Glu Lys Thr Pro Asp Glu Ala Ala Pro Leu Val Glu Arg
                245                 250                 255

Thr Pro Asp Thr Ala Glu Ser Leu Val Glu Lys Thr Pro Asp Glu Ala
            260                 265                 270

Ala Ser Leu Val Glu Gly Thr Ser Asp Lys Ile Gln Cys Leu Glu Lys
        275                 280                 285

Ala Thr Ser Gly Lys Phe Glu Gln Ser Ala Glu Glu Thr Pro Arg Glu
    290                 295                 300

Ile Thr Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Pro Ala
305                 310                 315                 320
```

Lys Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Asp Thr Pro
325 330 335

Arg Glu Ile Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp
340 345 350

Ala Ala Lys Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr
355 360 365

Pro Val Lys Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys
370 375 380

Val Leu Glu Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu
385 390 395 400

Ser Ser Thr Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser
405 410 415

Lys Gln Glu Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe
420 425 430

Glu Ser Ser Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln
435 440 445

Lys Val Met Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro
450 455 460

Ser Ala Phe Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys
465 470 475 480

Ala Phe Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe
485 490 495

Pro Pro Glu Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser
500 505 510

Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys
515 520 525

Ala Thr His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu
530 535 540

Ser Pro Asn Lys Asp Gly Leu Leu Lys Ala Thr Cys Gly Met Lys Val
545 550 555 560

Ser Ile Pro Thr Lys Ala Leu Glu Leu Lys Asp Met Gln Thr Phe Lys
565 570 575

Ala Glu Pro Pro Gly Lys Pro Ser Ala Phe Glu Pro Ala Thr Glu Met
580 585 590

Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr
595 600 605

Trp Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr
610 615 620

Glu Glu Asn Ser Trp Asp Thr Glu Ser Leu Cys Glu Thr Val Ser Gln
625 630 635 640

Lys Asp Val Cys Leu Pro Lys Ala Ala His Gln Lys Glu Ile Asp Lys
645 650 655

Ile Asn Gly Lys Leu Glu Gly Ser Pro Val Lys Asp Gly Leu Leu Lys
660 665 670

Ala Asn Cys Gly Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu

```
        675                 680                 685

Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala
    690                 695                 700

Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu
705                 710                 715                 720

Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser
                725                 730                 735

Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser
            740                 745                 750

Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr
        755                 760                 765

His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro
    770                 775                 780

Asp Asn Asp Gly Phe Leu Lys Ala Pro Cys Arg Met Lys Val Ser Ile
785                 790                 795                 800

Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu
                805                 810                 815

Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys
            820                 825                 830

Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg
        835                 840                 845

Ala Asp Gln Met Phe Pro Ser Glu Ser Lys Gln Lys Lys Val Glu Glu
    850                 855                 860

Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu Thr Val Ser Gln Lys Asp
865                 870                 875                 880

Val Cys Val Pro Lys Ala Thr His Gln Lys Glu Met Asp Lys Ile Ser
                885                 890                 895

Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser Lys Ile Leu Asp Thr Val
            900                 905                 910

His Ser Cys Glu Arg Ala Arg Glu Leu Gln Lys Asp His Cys Glu Gln
        915                 920                 925

Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys Phe Cys Val Leu Lys
    930                 935                 940

Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln
945                 950                 955                 960

Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu Thr Leu Asn
                965                 970                 975

Gln Glu Glu Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn Glu Lys Ile
            980                 985                 990

Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His Arg Lys Glu Leu Glu
        995                 1000                1005

Val Lys Gln Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu
    1010                1015                1020

Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser His Thr His Glu Asn
1025                1030                1035                1040
```

Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala
1045 1050 1055

Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
1060 1065 1070

Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
1075 1080 1085

Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg
1090 1095 1100

Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr
1105 1110 1115 1120

Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu
1125 1130 1135

Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp
1140 1145 1150

His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His
1155 1160 1165

Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser
1170 1175 1180

Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala
1185 1190 1195 1200

Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp
1205 1210 1215

Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln
1220 1225 1230

Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn
1235 1240 1245

Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp
1250 1255 1260

Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln
1265 1270 1275 1280

Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile
1285 1290 1295

Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu
1300 1305 1310

Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile
1315 1320 1325

Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Asn Ser
1330 1335 1340

<210> 23
<211> 24
<212> DNA
<213> Homo sapiens
<220>
<400> 23
aatgggaa4a agagctctgc ag 22

<210> 25

<211> 23
<212> DNA
<213> Homo sapiens
<220>
<400> 25
gggtcatctg aagttcagca ttc 23

<210> 26
<211> 3673
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 439, 473, 1789
<400> 26
caagagcttg gcgatacaga aatttctgct ggtgttgggg cgggtgcggg aactgaagac 60

gggcgagtgc gagccggggg cgggtgctgg ggaagggtaa gcgggaagcg agggcgaggg 120

gtaggggctg gggaagggcg agcgggaggc gcgggctctc tctagcaggg ggctgcagcc 180

atgaagaggc tcttagctgc cgctggcaag ggcgtgcggg gcccggagcc cccgaacccc 240

ttcagcgaac gggtctacac tgagaaggac tacgggacca tctacttcgg ggatctaggg 300

aagatccata cagctgcctc ccggggccaa gtccagaagc tggagaagat gacagtaggg 360

aagaagcccg tcaacctgaa caaaagagat atgaagaaga ggactgctct acactgggcc 420

tgtgtcaatg gccatgcana agtagtaaca tttctggtag acagaaagtg ccngcttaat 480

gtccttgatg gcgaagggag gacacctctg atgaaggctc tacaatgcga gagggaagct 540

ttgtgcaaat attctcatag atgctggtgc tgatctaaat tatgtagatg tgtatggcaa 600

cacggctctc cattatgccg tttatagtga gaatttatta atggtggcaa cactgctgtc 660

ctatggtgca gtcatcgagg tgcaaaacaa ggctagcctc acaccccttt tactggccat 720

acagaaaaga agcaagcaaa ctgtggaatt tttactaaca aaaaatgcaa atgcaaacgc 780

atttaatgag tctaaatgca cagccctcat gcttgccata tgtgaaggct catcagagat 840

agtcggcatg cttcttcagc aaaatgttga cgtctttgct gaagacatac atggaataac 900

tgcagaacgt tatgctgctg ctcgtggagt taattacatt catcaacaac ttttggaaca 960

tatacgaaaa ttacctaaaa atcctcaaaa taccaatcca gaaggaacat ctacaggaac 1020

acctgatgag gctgcaccct tggcggaaag aacacctgac acggctgaaa gcttgctgga 1080

aaaaacacct gacgaggctg cacgcttggt ggagggaacg tctgccaaaa ttcaatgtct 1140

ggggaaagca acatctggaa agtttgaaca gtcaacagaa gaaacaccta ggaaaatttt 1200

gaggcctaca aaagaaacat ctgagaaatt ttcatggcca gcaaaagaaa gatctaggaa 1260

gatcacatgg gaggaaaaag aaacatctgt aaagactgaa tgcgtggcag gagtaacacc 1320

taataaaact gaagttttgg aaaaaggaac atctaatatg attgcatgtc ctacaaaaga 1380

aacatctaca aaagcaagta caaatgtgga tgtgagttct gtagagccta tattcagtct 1440

ttttggcaca cggactattg aaaattcaca gtgtacaaaa gttgaggaag actttaatct 1500

tgctaccaag attatctcta agagtgctgc acagaattat acgtgtttac ctgatgctac 1560

atatcaaaaa gatatcaaaa caataaatca caaaatagaa gatcagatgt tcccatcaga 1620

atccaaacga gaggaagatg aagaatattc ttgggattct gggagtctct ttgagagttc 1680

tgcaaagact caagtgtgta tacctgagtc tatgtatcag aaagtaatgg agataaatag 1740

agaagtagaa gagcttcctg agaagccatc tgccttcaag cctgccgtng aaatgcaaaa 1800

gactgttcca aataaagcct ttgaattgaa gaatgaacaa acattgagag cagctcagat 1860

gttcccatca gaatccaaac aaaaggacga tgaagaaaat tcttgggatt ctgagagtcc 1920

ctgtgagacg gtttcacaga aggatgtgta tttacccaaa gctacacatc aaaaagaatt 1980

cgatacctta agtggaaaat tagaagagtc tcctgttaaa gatggtcttc tgaagcctac 2040

ctgtggaagg aaagtttctc ttccaaataa agccttagaa ttaaaggaca gagaaacatt 2100

caaagcagag tctcctgata aagatggtct tctgaagcct acctgtggaa ggaaagtttc 2160

tcttccaaat aaagccttag aattaaagga cagagaaaca ctcaaagcag agtctcctga 2220

taatgatggt cttctgaagc ctacctgtgg aaggaaagtt tctcttccaa ataaagcttt 2280

agaattgaag gacagagaaa cattcaaagc agctcagatg ttcccatcag aatccaaaca 2340

aaaggatgat gaagaaaatt cttgggattt tgagagtttc cttgagactc tcttacagaa 2400

tgatgtgtgt ttacccaagg ctacacatca aaaagaattc gataccttaa gtggaaaatt 2460

agaagagtct cctgataaag atggtcttct gaagcctacc tgtggaatga aaatttctct 2520

tccaaataaa gccttagaat tgaaggacag agaaacattc aaagcagagg atgtgagttc 2580

tgtagagtcc acattcagtc tttttggcaa accgactact gaaaattcac agtctacaaa 2640

agttgaggaa gactttaatc ttactaccaa ggagggagca acaaagacag taactggaca 2700

acaggaacgt gatattggca ttattgaacg agctccacaa gatcaaacaa ataagatgcc 2760

cacatcagaa ttaggaagaa aagaagatac aaaatcaact tcagattctg agattatctc 2820

tgtgagtgat acacagaatt atgagtgttt acctgaggct acatatcaaa aagaaataaa 2880

gacaacaaat ggcaaaatag aagagtctcc tgaaaagcct tctcactttg agcctgccac 2940

tgaaatgcaa aactctgttc caaataaagg cttagaatgg aagaataaac aaacattgag 3000

agcagattca actaccctat caaaaatctt ggatgcactt ccttcttgtg aaagaggaag 3060

ggaacttaaa aaagataact gtgaacaaat tacagcaaaa atggaacaaa tgaaaaataa 3120

gttttgtgta ctacaaaagg aactgtcaga agcgaaagaa ataaaatcac agttagagaa 3180

ccaaaaagct aaatgggaac aagagctctg cagtgtgaga ttgcctttaa atcaagaaga 3240

agagaagaga agaaatgtcg atatattaaa agaaaaaatt agacccgaag agcaacttag 3300

gaaaaagtta gaagtgaaac accaacttga acagactctc agaatacaag atatagaatt 3360

gaaaagtgta acaagtaatt tgaatcaggt ttctcacact catgaaagtg aaaatgatct 3420

ctttcatgaa aattgcatgt tgaaaaagga aattgccatg ctaaaactgg aagtagccac 3480

actgaaacat caacaccagg tgaaggaaaa taaatacttt gaggacatta agattttaca 3540

agaaaagaat gctgaacttc aaatgaccct aaaactgaaa cagaaaacag taacaaaaag 3600

ggcatctcag tatagagagc agcttaaagt tctgacggca gagaacacga tgctgacttc 3660

taaattgaag gaa 3673

<210> 27
<211> 1011
<212> PRT
<213> Homo sapiens
<220>
<400> 27

```
Met Val Ala Thr Leu Leu Ser Tyr Gly Ala Val Ile Glu Val Gln Asn
1               5                  10                  15

Lys Ala Ser Leu Thr Pro Leu Leu Leu Ala Ile Gln Lys Arg Ser Lys
            20                  25                  30

Gln Thr Val Glu Phe Leu Leu Thr Lys Asn Ala Asn Ala Asn Ala Phe
        35                  40                  45

Asn Glu Ser Lys Cys Thr Ala Leu Met Leu Ala Ile Cys Glu Gly Ser
    50                  55                  60

Ser Glu Ile Val Gly Met Leu Leu Gln Gln Asn Val Asp Val Phe Ala
65                  70                  75                  80

Glu Asp Ile His Gly Ile Thr Ala Glu Arg Tyr Ala Ala Ala Arg Gly
                85                  90                  95

Val Asn Tyr Ile His Gln Gln Leu Leu Glu His Ile Arg Lys Leu Pro
            100                 105                 110

Lys Asn Pro Gln Asn Thr Asn Pro Glu Gly Thr Ser Thr Gly Thr Pro
        115                 120                 125

Asp Glu Ala Ala Pro Leu Ala Glu Arg Thr Pro Asp Thr Ala Glu Ser
    130                 135                 140

Leu Leu Glu Lys Thr Pro Asp Glu Ala Ala Arg Leu Val Glu Gly Thr
145                 150                 155                 160

Ser Ala Lys Ile Gln Cys Leu Gly Lys Ala Thr Ser Gly Lys Phe Glu
                165                 170                 175

Gln Ser Thr Glu Glu Thr Pro Arg Lys Ile Leu Arg Pro Thr Lys Glu
            180                 185                 190

Thr Ser Glu Lys Phe Ser Trp Pro Ala Lys Glu Arg Ser Arg Lys Ile
        195                 200                 205

Thr Trp Glu Glu Lys Glu Thr Ser Val Lys Thr Glu Cys Val Ala Gly
    210                 215                 220

Val Thr Pro Asn Lys Thr Glu Val Leu Glu Lys Gly Thr Ser Asn Met
225                 230                 235                 240

Ile Ala Cys Pro Thr Lys Glu Thr Ser Thr Lys Ala Ser Thr Asn Val
                245                 250                 255

Asp Val Ser Ser Val Glu Pro Ile Phe Ser Leu Phe Gly Thr Arg Thr
            260                 265                 270

Ile Glu Asn Ser Gln Cys Thr Lys Val Glu Glu Asp Phe Asn Leu Ala
        275                 280                 285

Thr Lys Ile Ile Ser Lys Ser Ala Ala Gln Asn Tyr Thr Cys Leu Pro
    290                 295                 300
```

```
Asp Ala Thr Tyr Gln Lys Asp Ile Lys Thr Ile Asn His Lys Ile Glu
305                 310                 315                 320

Asp Gln Met Phe Pro Ser Glu Ser Lys Arg Glu Glu Asp Glu Glu Tyr
                325                 330                 335

Ser Trp Asp Ser Gly Ser Leu Phe Glu Ser Ser Ala Lys Thr Gln Val
            340                 345                 350

Cys Ile Pro Glu Ser Met Tyr Gln Lys Val Met Glu Ile Asn Arg Glu
        355                 360                 365

Val Glu Glu Leu Pro Glu Lys Pro Ser Ala Phe Lys Pro Ala Val Glu
    370                 375                 380

Met Gln Lys Thr Val Pro Asn Lys Ala Phe Glu Leu Lys Asn Glu Gln
385                 390                 395                 400

Thr Leu Arg Ala Ala Gln Met Phe Pro Ser Glu Ser Lys Gln Lys Asp
                405                 410                 415

Asp Glu Glu Asn Ser Trp Asp Ser Glu Ser Pro Cys Glu Thr Val Ser
            420                 425                 430

Gln Lys Asp Val Tyr Leu Pro Lys Ala Thr His Gln Lys Glu Phe Asp
        435                 440                 445

Thr Leu Ser Gly Lys Leu Glu Glu Ser Pro Val Lys Asp Gly Leu Leu
    450                 455                 460

Lys Pro Thr Cys Gly Arg Lys Val Ser Leu Pro Asn Lys Ala Leu Glu
465                 470                 475                 480

Leu Lys Asp Arg Glu Thr Phe Lys Ala Glu Ser Pro Asp Lys Asp Gly
                485                 490                 495

Leu Leu Lys Pro Thr Cys Gly Arg Lys Val Ser Leu Pro Asn Lys Ala
            500                 505                 510

Leu Glu Leu Lys Asp Arg Glu Thr Leu Lys Ala Glu Ser Pro Asp Asn
        515                 520                 525

Asp Gly Leu Leu Lys Pro Thr Cys Gly Arg Lys Val Ser Leu Pro Asn
    530                 535                 540

Lys Ala Leu Glu Leu Lys Asp Arg Glu Thr Phe Lys Ala Ala Gln Met
545                 550                 555                 560

Phe Pro Ser Glu Ser Lys Gln Lys Asp Asp Glu Glu Asn Ser Trp Asp
                565                 570                 575

Phe Glu Ser Phe Leu Glu Thr Leu Leu Gln Asn Asp Val Cys Leu Pro
            580                 585                 590

Lys Ala Thr His Gln Lys Glu Phe Asp Thr Leu Ser Gly Lys Leu Glu
        595                 600                 605

Glu Ser Pro Asp Lys Asp Gly Leu Leu Lys Pro Thr Cys Gly Met Lys
    610                 615                 620

Ile Ser Leu Pro Asn Lys Ala Leu Glu Leu Lys Asp Arg Glu Thr Phe
625                 630                 635                 640

Lys Ala Glu Asp Val Ser Ser Val Glu Ser Thr Phe Ser Leu Phe Gly
                645                 650                 655

Lys Pro Thr Thr Glu Asn Ser Gln Ser Thr Lys Val Glu Glu Asp Phe
```

```
            660                 665                 670

Asn Leu Thr Thr Lys Glu Gly Ala Thr Lys Thr Val Thr Gly Gln Gln
        675                 680                 685

Glu Arg Asp Ile Gly Ile Ile Glu Arg Ala Pro Gln Asp Gln Thr Asn
    690                 695                 700

Lys Met Pro Thr Ser Glu Leu Gly Arg Lys Glu Asp Thr Lys Ser Thr
705                 710                 715                 720

Ser Asp Ser Glu Ile Ile Ser Val Ser Asp Thr Gln Asn Tyr Glu Cys
                725                 730                 735

Leu Pro Glu Ala Thr Tyr Gln Lys Glu Ile Lys Thr Thr Asn Gly Lys
            740                 745                 750

Ile Glu Glu Ser Pro Glu Lys Pro Ser His Phe Glu Pro Ala Thr Glu
        755                 760                 765

Met Gln Asn Ser Val Pro Asn Lys Gly Leu Glu Trp Lys Asn Lys Gln
    770                 775                 780

Thr Leu Arg Ala Asp Ser Thr Thr Leu Ser Lys Ile Leu Asp Ala Leu
785                 790                 795                 800

Pro Ser Cys Glu Arg Gly Arg Glu Leu Lys Lys Asp Asn Cys Glu Gln
                805                 810                 815

Ile Thr Ala Lys Met Glu Gln Met Lys Asn Lys Phe Cys Val Leu Gln
            820                 825                 830

Lys Glu Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln
        835                 840                 845

Lys Ala Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu Pro Leu Asn
    850                 855                 860

Gln Glu Glu Glu Lys Arg Arg Asn Val Asp Ile Leu Lys Glu Lys Ile
865                 870                 875                 880

Arg Pro Glu Glu Gln Leu Arg Lys Lys Leu Glu Val Lys His Gln Leu
                885                 890                 895

Glu Gln Thr Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val Thr Ser
            900                 905                 910

Asn Leu Asn Gln Val Ser His Thr His Glu Ser Glu Asn Asp Leu Phe
        915                 920                 925

His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys Leu Glu
    930                 935                 940

Val Ala Thr Leu Lys His Gln His Gln Val Lys Glu Asn Lys Tyr Phe
945                 950                 955                 960

Glu Asp Ile Lys Ile Leu Gln Glu Lys Asn Ala Glu Leu Gln Met Thr
                965                 970                 975

Leu Lys Leu Lys Gln Lys Thr Val Thr Lys Arg Ala Ser Gln Tyr Arg
            980                 985                 990

Glu Gln Leu Lys Val Leu Thr Ala Glu Asn Thr Met Leu Thr Ser Lys
        995                 1000                1005

Leu Lys Glu
    1010
```

<210> 28
<211> 23
<212> DNA
<213> Homo sapiens
<220>
<400> 28
tctcatagat gctggtgctg atc 23

<210> 29
<211> 24
<212> DNA
<213> Homo sapiens
<220>
<400> 29
cccagacatt gaattttggc agac 24

United States Patent & Trademark Office

Office of Initial Patent Examination -- Scanning Division

Application deficiencies were found during scanning:

☐ Page(s) 2 of Drawings (Document title) were not present for scanning.

☐ Page(s) ______ of ______ (Document title) were not present for scanning.

☐ Scanned copy is best available.